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^{1}H AND ^{13}C CHEMICAL SHIFTS: UNEXPLAINED ANALOGIES AND ANOMALIES

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Cyclohexane and hetero-analogs of cyclohexane, such as 1,3-dioxane, 1,3-dithiane, etc. present relatively rigid frameworks[1] in which the effect of substituents and heteroatoms, e.g., on spectral properties, can be systematically studied. Among the classical investigations in this area have been those of Lemieux, Bernstein and coworkers[2] on proton nmr spectroscopy and those of Grant and coworkers[3] on ^{13}C nuclear magnetic resonance.

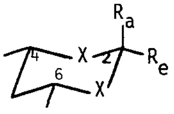
Differences in chemical shifts of diastereotopic protons, i.e., protons in chemically identical but stereochemically distinct environments, are customarily interpreted in terms of differences in diamagnetic anisotropy of C-C or C-X (X = heteroatom) bonds which are differently located with respect to the diastereotopic nuclei.[4] Thus the fact that an axial proton in a cyclohexane resonates upfield of the corresponding equatorial one is usually explained in terms of the magnetic anisotropy of the C_β-C_γ bond. In contrast, the upfield ^{13}C shift of axial methyl groups in methylcyclohexanes compared to equatorial ones has been accounted for[3,5] in terms of the steric interaction of the protons of the methyl group with the syn-axial ring protons ("steric shift").

We wish to draw attention here to several instances where

(1) diamagnetic bond anisotropies alone do not properly account for differences in chemical shifts of diastereotopic protons and

(2) there is a close analogy between shift differences of diastereotopic protons on one hand and diastereotopic methyl groups on the other so as to suggest a common origin of the two.[20]

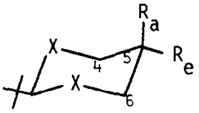
In Table 1 are summarized the proton shifts (1, R = H) and the ^{13}C methyl shifts (1, R = CH_3) of axial and equatorial substituents in cyclohexane (X = CH_2), 1,3-dioxane (X = O) and 1,3-dithiane (X = S) at position 2 (referring to the hetero-substituted systems).



X = CH_2, O, S

1

$R_e = R_a = H$
or
$R_e = CH_3$, $R_a = H$
or
$R_e = H$, $R_a = CH_3$



X = CH_2, O, S

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Table 1. Chemical Shifts[a] for Axial and Equatorial Substituents in 1.

		Protons (R = H)			Methyl Carbons (R = CH_3)			
X	Item No.	H_e	H_a	Δ[b]	Item No.	Me_e	Me_a	Δ[b]
CH_2	1[6]	(1.67)[c]	(1.12)[c]	(0.55)[c]	4[8]	22.8	18.9	3.9
O	2[7]	4.87	4.53	0.34	5[d]	21.2	17.0	4.2
S	3[d]	3.48	4.00	-0.52	6[9]	20.2	25.4	-5.2

[a]In ppm downfield from TMS. [b]R_e-shift minus R_a-shift. [c]These values are for H-4 in a highly deuterated *t*-butylcyclohexane.[6] The values for 1, R = H, X = CH_2 are not available. [d]This work.

These data should be compared to those for 2, shown in Table 2, which refer to the 5-position in the hetero-substituted systems.

Table 2. Chemical Shifts[a] for Axial and Equatorial Substituents in 2.

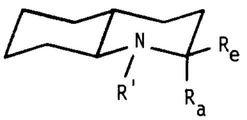
		Protons (R = H)			Methyl Carbons (R = CH_3)			
X	Item No.	H_e	H_a	Δ[b]	Item No.	Me_e	Me_a	Δ[b]
CH_2	7[6]	1.67	1.12	0.55	10[8]	22.7	17.5	5.2
O	8[10]	1.24	1.96	-0.72	11[11]	12.4	15.9	-3.5
S	9[d]	2.09[c]	1.81[c]	0.28	12[9]	22.2	16.4	5.8

[a]In ppm downfield from TMS. [b]R_e-shift minus R_a-shift. [c]Approximative values; spectrum has not yet been completely analyzed.[12] [d]This work.

We note, first of all, that in 1,3-dioxane H-5a is downfield from H-5e (item 8, Table 2) but this "anomaly" is not found for H-2e and H-2a (item 2 in Table 1). In contrast, in 1,3-dithiane, the "anomaly" occurs at H-2a which is downfield from H-2e (Table 1, item 3) whereas the corresponding H-5's (Table 2, item 9) are "normal."[13] These reversals cannot readily be ascribed to the anisotropy of the X-C_4 and X-C_6 (X = O or S) bonds, since these bonds have nearly the same disposition vis-ā-vis corresponding protons at C-2 and at C-5, so that if a reversal of the normal upfield shift of H_a occurs at one site, it should also occur at the other.

Secondly we note that the same inversion of the "normal" upfield-downfield relation of axial and equatorial shifts also occurs for the ^{13}C signals of the methyl groups: In the 1,3-dioxane, Me-2a *vs*. Me-2e (item 5, Table 1) is "normal" but Me-5a *vs*. Me-5e (item 11, Table 2) is "anomalous." Contrariwise (but preserving the analogy with the proton situation), Me-2a *vs*. Me-2e (item 6, Table 1) is "anomalous" in 1,3-dithiane whereas Me-5a *vs*. Me-5e (item 12, Table 2) is "normal." It would almost appear as if the same factor which brings about reversal of the normal upfield shift of the axial nucleus in the ^{13}C spectrum is also responsible for the same reversal in the proton spectrum. We believe that this factor is *not* bond anisotropy;[14] we can only speculate that a paramagnetic shift (unusual in ^1H spectra of saturated compounds) occurs in the compounds bearing hetero-atoms with their unshared electron pairs; or, perhaps, that the effect observed is due to charge alternation effects.[15]

Finally we draw attention to an apparent effect of lone pairs on anti-periplanar nuclei in amines (3, 4; test nuclei R = H or CH_3). It has been known for some time that protons in such positions are shifted strongly upfield.[16] The data in Table 3 not only confirm this for the case



3

$R_e = R_a = H$
or
$R_e = CH_3$, $R_a = H$
or
$R_e = H$, $R_a = CH_3$

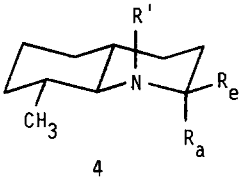


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Table 3. Chemical Shifts[a] of Substituents at C-2 (R_e, R_a) in N-Methyl-trans-decahydroquinolines (3, 4; R' = CH_3)

Compound	R = H[17a]		R = CH_3		Ref.
	H_e	H_a	Me_e	Me_a	
3, R' = CH_3	2.73	$\underline{1.95}$	21.93	$\underline{9.08}$	17b
4, R' = CH_3	2.76	2.85	20.67	18.18	b

[a] In ppm, downfield from TMS. [b] This work.

where R = H but show an exactly corresponding shift when R = CH_3 (underlined entries). (It should be noted that compounds 3 have nearly exclusively equatorial N-CH_3 because of the substantial inherent preference of the N-Me group for the equatorial position.[18] Compounds 4, in contrast have axial N-Me groups because of the constraint provided by the equatorial C-methyl group at C-8.[18])

Once again, the data in Table 3 suggest a common origin of the upfield shift for ^{1}H and ^{13}C.[20] No such upfield shift occurs when the unshared pair is syn-clinal to the test nucleus (4). Thus one might be inclined to ascribe the upfield shift to an anti-periplanar effect of the lone pair, but such an interpretation must be viewed with caution. In the N-H analogs, R' = H, there is nearly no difference in either proton shifts (R = H, 3: H_e, 3.04; H_a, 2.62 ppm; 4: H_e, 3.08; H_a, 2.63 ppm) or ^{13}C shifts (R = CH_3, 3: Me_e, 22.95; Me_a, 18.62 ppm; 4: Me_e, 23.04; Me_a, 18.78 ppm, analog of 3 with axial Me group at C-8: Me_e, 23.01; Me_a, 18.22 ppm). Since the equilibrium constant for axial $\rightleftharpoons$ equatorial NH in 3, R' = H, must be near unity,[18] this finding means either that the addition of equatorial or axial methyl groups at C-8 does not affect this equilibrium (which appears unlikely) or that the test nuclei (^{1}H, ^{13}C) at C-2 are insensitive to the position of the lone pair on nitrogen when the substituent on nitrogen is H rather than CH_3 (contrary to ref. 16b).

We believe that the various anomalies and analogies reported in this communication are due to a common cause[20] and hope that drawing attention to them will aid in the as yet elusive theoretical interpretation of the chemical shift.

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References and Footnotes

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