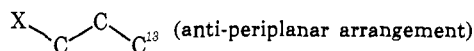


# Carbon-13 Magnetic Resonance. Upfield Shifts Caused by Nitrogen, Oxygen, and Fluorine Atoms Located at the $\gamma$ Position and Anti-Periplanar to the Nucleus Observed

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**Abstract:** Upfield shifts in the magnetic resonance of the marked carbon-13 nucleus are found in the conformational array



when X = N, O, or F (compared with X = C or H) except when X is located at the bridgehead of a bicyclic compound. No appreciable shifts are found for X = Cl or S.

Carbon-13 magnetic resonance is now generally recognized as one of the most useful spectroscopic techniques available for stereochemical assignment and the elucidation of structure. These applications are, for the most part, based on empirical correlations of carbon-13 shieldings and molecular geometry.<sup>2-4</sup> The upfield shift observed for the resonance of a carbon which is gauche to another carbon<sup>5-10</sup> or heteroatom<sup>9-15</sup> at the  $\gamma$  position (Figure 1, A) relative to the resonance of an analogous carbon in the anti conformation (Figure 1, B) is of particular utility for stereochemical assignment.<sup>2-15</sup> This well-documented  $\gamma$  effect is ascribed<sup>16</sup> to steric perturbation which is thought to polarize the <sup>13</sup>C-H bonds of the encumbered groups such that the carbon nucleus is shielded and the attached protons are deshielded. It would appear, however, in light of the recent report<sup>17</sup> of deshielding  $\delta$  effects in molecules beset with severe syn-axial interactions with atoms other than hydrogen, that additional mechanisms may have to be called upon to explain <sup>13</sup>C shifts in such crowded situations. Clearly, the interpretation of small shift changes in complex molecules containing a number of different atoms must be approached with caution until empirical correlations are extended to a wider variety of systems and are better understood theoretically.

For these reasons, we were intrigued by the apparently anomalous carbon-13 shieldings which we observed<sup>18</sup> for the 5-methyl carbons of *cis*- and *trans*-2-*tert*-butyl-5-methyl-1,3-dioxane (A and B, Figure 2). Contrary to the trend found for methylcyclohexanes<sup>2-7</sup> (Figure 2, C and D) and substituted decalins,<sup>8</sup> the equatorial 5-methyl resonance of the *trans* isomer is found at higher field ( $\delta$  12.4 ppm) than the axial 5-methyl resonance of its epimer ( $\delta$  15.9 ppm). Both the axial and equatorial 5-methyl carbons in the dioxane system<sup>18</sup> resonate at considerably higher field than similar carbons in the methylcyclohexanes,<sup>2-7</sup> but the incremental upfield shift is much larger (-10.9 ppm) for equatorial CH<sub>3</sub> than for axial CH<sub>3</sub> (-3.6 ppm). Apparently the ring oxygen atoms profoundly affect the chemical shifts of not only gauche (or syn-clinal) but also anti (or anti-periplanar)  $\gamma$  carbon nuclei. Unfortunately, although the carbon-13 magnetic resonance spectra of a number of molecules containing hetero substituents have been recorded,<sup>2-4</sup> there is a dearth of systematic knowledge concerning the conformational factors which affect carbon-13

shieldings in systems possessing such heteroatoms. Two notable exceptions are the investigation of carbon-13 shieldings in substituted cyclohexanols<sup>10,11</sup> and heterosubstituted norbornanes<sup>9</sup> by Roberts and coworkers. Both of these studies indicate that appreciable upfield  $\gamma$  shifts may result when certain heteroatoms are located anti to a carbon nucleus. To assess the generality of this phenomenon, we undertook a systematic investigation of the conformational dependence of carbon-13 shieldings in molecules of well-defined stereochemistry possessing heteroatoms gauche and anti to carbon nuclei.

The results of this study (Table I) clearly demonstrate that a carbon atom located anti to a second-row heteroatom in the  $\gamma$  position (Figure 1, B, X = N, O, F) generally (*vide infra*) resonates at significantly higher field than an analogous nucleus anti to a methyl or methylene group or to a third-row heteroatom (Figure 1, B, X = CH<sub>3</sub>, -CH<sub>2</sub>-, S, Cl). In addition, the data (Table II) tend to confirm the conclusion reached in earlier studies<sup>19</sup> that a gauche heteroatom (Figure 1, A, X = N, O, F, S, Cl) results in an upfield shift of a carbon-13 signal greater than the upfield shift caused by a methyl or methylene group. However, the incremental upfield shift (Figure 1, A, X = N, O, F, S, Cl as compared with X = CH<sub>3</sub> or CH<sub>2</sub>) on the gauche carbon is generally *less* than the corresponding incremental upfield shift on the anti carbon (Figure 1, B).

## Results

The chemical shifts of carbon nuclei oriented anti to  $\gamma$  heteroatoms are given in Table I in parts per million downfield from TMS. Recently, carbon-13 chemical shifts have been reported<sup>20-23</sup> for a wide variety of substituted piperidines in a number of solvents, and we have included these results in Table I to demonstrate the consistency of the upfield shift of a carbon anti to a  $\gamma$  nitrogen.

Table II contains the chemical shifts of carbon nuclei gauche to heteroatoms in a number of representative molecules. This table is not intended as an exhaustive compilation of gauche shieldings since the recent literature<sup>19</sup> abounds with additional examples. In this context, it should be noted that the C(4) resonance of a substituted piperidine is invariably found at higher field<sup>20-23</sup> than the resonance of an analogous carbon in a similarly substituted cyclohexane.<sup>5-7</sup>

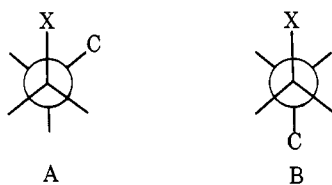


Figure 1.

In both Table I and Table II, the resonance of a particular carbon nucleus [ $\delta(^{13}\text{C})$ ], which is either anti or gauche to a heteroatom, is compared with the resonance of an analogous carbon in a reference system [ $\delta(^{13}\text{C ref})$ ]<sup>24</sup> in which the heteroatom(s) is (are) replaced by  $-\text{CH}_2-$  or  $-\text{CH}_3$  groups to give the  $\gamma$  effects of anti (Table I) and gauche (Table II) heteroatoms relative to the  $\gamma$  effects of methyl or methylene groups. However, since the  $\gamma_e$  effect of a  $-\text{CH}_2-$  or  $-\text{CH}_3$  group is negligible,<sup>2-7</sup> the  $\gamma$  effects of anti-periplanar heteroatoms may be effectively referenced with respect to hydrogen.

Inspection of the data in Table I reveals that second-row heteroatoms (N, O, F) cause significant upfield shifts<sup>25</sup> in the resonance of anti-periplanar carbon nuclei whereas, in contrast, third-row heteroatoms (S, Cl) demonstrate negligible (<1 ppm) anti effects. Additional examples and corroborative data may be gleaned from carbon-13 shifts of more complex molecules. For example, the C(1) resonances of both cholestan-3 $\beta$ -ol (37.6 ppm)<sup>10</sup> and its acetate (37.2 ppm)<sup>10</sup> are more shielded, by 1.6 and 2.0 ppm, than the C(1) resonance of parent cholestane (39.2 ppm);<sup>10</sup> the  $\gamma$  effects of anti-periplanar  $-\text{NH}_2$  and  $-\text{OH}$  are evident in the shifts reported by Conway, *et al.*,<sup>26</sup> for 14 trans-fused methyl 4,6-*O*-benzylidene-D-aldohexopyranosides which show a consistent shielding of 1.3 ppm by anti-periplanar  $-\text{NH}_2$  and a shielding of 1.6 ppm by anti-periplanar  $-\text{OH}$ ; a 2-hydroxyl group in the adamantane system shields the  $\gamma$  (anti) carbons by 1.1 ppm<sup>14</sup> (relative to adamantane), whereas a 2-chloro substituent has a negligible (+0.1 ppm)<sup>14</sup> effect on this resonance; finally, the C(6) resonance in isoborneol (34.9 ppm)<sup>13</sup> is 2.4 ppm to higher field than the C(6) resonance of parent bornane (37.3 ppm),<sup>13</sup> whereas the C(6) resonance of isbornyl chloride (36.6 ppm)<sup>13</sup> is only slightly shielded (0.7 ppm) relative to the parent.

To our knowledge, the only exceptions to the shielding  $\gamma$  effects of anti-periplanar second-row heteroatoms discussed above occur in systems having the heteroatom attached to a bridgehead carbon. The reported chemical shifts of 1-substituted bicyclo[2.2.2]octanes<sup>27</sup> and 1-substituted adamantanes<sup>14</sup> indicate that the resonance frequency of an anti-periplanar carbon in the 1-substituted compounds is found at lower field than that of an analogous carbon in the parent hydrocarbon for all hetero substituents.<sup>28</sup>

It is apparent from these results (Table I) that the tendency<sup>15</sup> to associate the observation of upfield shifts with the presence of gauche conformations is dangerous in systems possessing second-row heteroatoms. Stereochemical assignments based upon small shielding differences in such systems should be made with great caution since it would appear<sup>17,25</sup> that there may be a variety of conformationally dependent shielding mechanisms involved in the effect of N, O, and F substituents on carbon-13 chemical shifts. These results also raise important questions as to the origin of the  $\gamma$  anti effects of second-row heteroatoms. We shall return to this point below.

Inspection of items 56-75 (Table II) substantiates the contention<sup>19</sup> that gauche heteroatoms are generally more effective than methyl or methylene groups in producing upfield  $\gamma$  shifts. It is significant, therefore, that the axial 5-

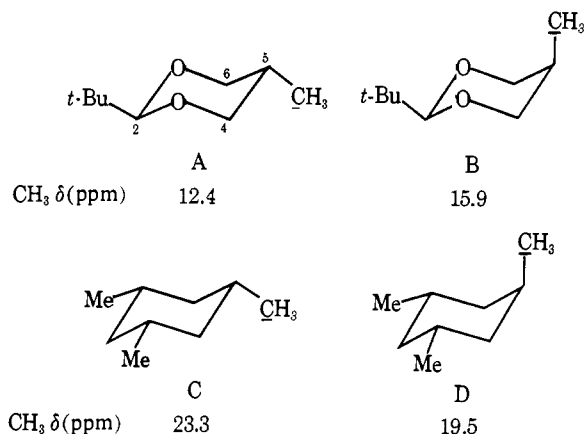


Figure 2.

methyl carbons of 2-*tert*-butyl- (item 55) and, to a lesser extent, 2-isopropyl-*N,N',5,5*-tetramethyl-1,3-diazane (item 54) resonate at lower field than the axial methyl carbon of 1,1,3-trimethylcyclohexane.<sup>5</sup> In contrast, the axial 5-methyl carbon of both the 2-methyl and 2-ethyl compounds is as shielded as the axial methyl carbon in the cyclohexane reference. The apparently anomalous  $\gamma$  effects observed for 2-*tert*-butyl- and 2-isopropyl-*N,N',5,5*-tetramethyl-1,3-diazane suggest that the gauche interactions experienced by the axial methyl group in 1,1,3-trimethylcyclohexane are relieved in these particular diazanes. In fact, consideration of the proton magnetic resonance data for this series of *N,N',5,5*-tetramethyl-1,3-diazanes has led to the conclusion<sup>29</sup> that, whereas the 2-methyl and 2-ethyl compounds exist in chair conformations,<sup>30</sup> the 2-isopropyl and 2-*tert*-butyl molecules adopt nonchair flexible conformations<sup>29</sup> presumably to relieve the severe nonbonded interactions between the isopropyl or *tert*-butyl and vicinal N- $\text{CH}_3$  groups.<sup>31</sup> Viewed in this light, the downfield shifts observed for items 54 and 55 relative to the axial methyl resonance of 1,1,3-trimethylcyclohexane<sup>5</sup> are entirely consistent with the less crowded environment of a pseudo-axial methyl group in a nonchair conformation<sup>32</sup> compared with an axial methyl group in a cyclohexane chair, and the carbon-13 magnetic resonance data thus complement the proton magnetic resonance results.<sup>29</sup>

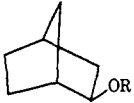
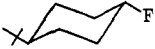
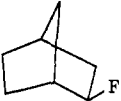
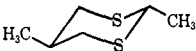





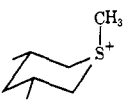
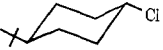
## Discussion

Any discussion of the  $\gamma$  anti effect can only be semiquantitative, because theoretical methods for characterizing the relatively small, long-range perturbations reported herein are marginal at best, *especially* when the interacting groups lack spatial proximity. Furthermore, there is no possibility to involve simple steric arguments which may still be important for  $\gamma$  gauche interactions. Several possible mechanisms used to account for other nmr data could be contributing to the  $\gamma$  anti shifts. These include (a)  $\sigma$ -bond polarization through the two intermediate carbon atoms, (b) electrostatic-field effect through space, (c) back-lobe interaction of the  $\text{sp}^3$ -hybridized orbitals on  $\text{C}_\gamma$  with those on  $\text{C}_\alpha$  used to bind the N, O, or F atom, and (d) hyperconjugative-type interaction of free-electron pairs centered on the N, O, and F atoms with the  $\text{C}_\alpha$ - $\text{C}_\beta$  bond accompanied by a subsequent alternation of the electron density at the  $\gamma$  anti-periplanar carbon. Mechanisms a and b are similar in kind and should relate directly to the electronegativity of the perturbing group. It is difficult, however, to ascribe the upfield shifts engendered by an anti-periplanar second-row heteroatom simply to substituent electronegativity<sup>9</sup> since both nitrogen and chlorine have the same electronegativity, and whereas anti-periplanar nitrogen results in an appreciable upfield

Table I. Shielding Effects (ppm) of Heteroatoms Anti-Periplanar to Carbon

Heteroatom	System					$\delta(^{13}\text{C})$ , <sup>e</sup> ppm from TMS	$\delta(^{13}\text{C})$ ref), <sup>b</sup> ppm from TMS	$\gamma$ effect, <sup>c</sup> $\delta(^{13}\text{C}) - \delta(^{13}\text{C} \text{ ref})$	Item
Nitrogen									
	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	R <sub>4</sub>	R <sub>5</sub>	20.0, 19.9, <sup>d</sup> 20.0, <sup>e</sup> 19.8 <sup>f</sup>	23.3	-3.4	1
	H	H	H	CH <sub>3</sub>	H	19.0, 17.8, <sup>d</sup> 18.9 <sup>f</sup>	23.3	-4.7	2
	H	H	H	CH <sub>3</sub>	CH <sub>3</sub>	20.4, 19.9, <sup>e</sup> 19.3 <sup>g</sup>	23.4	-3.6	3
	H	H	H	CH <sub>3</sub>	CH <sub>3</sub>	18.8	23.4	-4.6	4
	H	CH <sub>3</sub>	H	CH <sub>3</sub>	H	20.0, 19.8 <sup>d</sup>	23.4	-3.5	5
	H	CH <sub>3</sub>	H	CH <sub>3</sub>	H	17.9 <sup>d</sup>	23.4	-5.5	6
	H	CH <sub>3</sub>	H	CH <sub>3</sub>	CH <sub>3</sub>	19.6 <sup>e</sup>	23.4	-3.8	7
	H	H	CH <sub>3</sub>	H	CH <sub>3</sub>	19.4 <sup>g</sup>	23.3	-3.9	8
	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>						
	CH <sub>3</sub>	CH <sub>3</sub>	CH <sub>3</sub>			27.0 or 25.9	34.3	-7.3 or -8.4	9
	C <sub>2</sub> H <sub>5</sub>	CH <sub>3</sub>	CH <sub>3</sub>			26.9 or 25.7	34.3	-7.4 or -8.6	10
	CH(CH <sub>3</sub> ) <sub>2</sub>	CH <sub>3</sub>	CH <sub>3</sub>			27.7 or 26.4	34.3	-6.6 or -7.9	11
	C(CH <sub>3</sub> ) <sub>3</sub>	CH <sub>3</sub>	CH <sub>3</sub>			28.4 to 29.2	34.3	-5.1 to -5.9	12
					C(3,5) = 26.4	28.0	-1.7	13	
					C(3,5) = 25.7	28.0	-2.3	14	
					C(6) = 27.0 <sup>h</sup>	29.0	-2.0	15	
Oxygen									
	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	R <sub>4</sub>					
	H	H	CH <sub>3</sub>	H		13.1	23.3	-10.2	16
	CH <sub>3</sub>	CH <sub>3</sub>	CH <sub>3</sub>	H		13.5	22.4	-8.9	17
	H	CH <sub>3</sub>	CH <sub>3</sub>	H		12.1	23.3	-11.2	18
	H	C(CH <sub>3</sub> ) <sub>3</sub>	CH <sub>3</sub>	H		12.4 <sup>i</sup>	23.3	-10.9	19
	H	C(CH <sub>3</sub> ) <sub>3</sub>	CH <sub>3</sub>	CH <sub>3</sub>		22.2 <sup>i</sup>	32.9	-10.7	20
	H	C(CH <sub>3</sub> ) <sub>3</sub>	CH <sub>2</sub> CH <sub>3</sub>	H		21.5	30.7	-9.4	21
	H	C(CH <sub>3</sub> ) <sub>3</sub>	CH(CH <sub>3</sub> ) <sub>2</sub>	H		27.7			22
	H	H	C(CH <sub>3</sub> ) <sub>3</sub>	H		30.7 <sup>i</sup>	32.4	-1.7	23
	H	CH <sub>3</sub>	C(CH <sub>3</sub> ) <sub>3</sub>	H		30.5 <sup>i</sup>	32.4	-1.9	24
	CH <sub>3</sub>	CH <sub>3</sub>	C(CH <sub>3</sub> ) <sub>3</sub>	H		31.0 <sup>i</sup>	32.4	-1.4	25
	H	C(CH <sub>3</sub> ) <sub>3</sub>	C(CH <sub>3</sub> ) <sub>3</sub>	H		30.0 <sup>i</sup>	32.3	-2.3	26
	H	C <sub>6</sub> H <sub>5</sub>	C(CH <sub>3</sub> ) <sub>3</sub>	H		30.5 <sup>i</sup>	32.4	-1.9	27
						3,5-CH <sub>3</sub> = 17.5	23.4	-5.9	28
						C(5) = 26.4	34.7	-8.3	29
						C(7) = 24.9	27.2	-2.3	30
	R = H					C(3,5) = 25.7 <sup>i</sup>	28.0	-2.3	31
	R = Ac					C(3,5) = 25.9 <sup>i</sup>	28.0	-2.1	32
R = CH <sub>3</sub>					C(3,5) = 25.6 <sup>k</sup>	28.0	-2.4	33	
R = H					C(3) = 46.7 <sup>k</sup>	48.8	-2.1	34	
					C(5) = 24.4 <sup>k</sup>	27.7	-3.3	35	
R = Ac					C(3) = 46.6 <sup>k</sup>	48.8	-2.2	36	
					C(5) = 24.2 <sup>k</sup>	27.7	-3.5	37	
R = CH <sub>3</sub>					C(3) = 46.7 <sup>k</sup>	48.8	-2.1	38	

Table I (Continued)

Heteroatom	System	$\delta(^{13}\text{C})^a$ , ppm from TMS	$\delta(^{13}\text{C}$ ref) <sup>b</sup> , ppm from TMS	$\gamma$ effect, <sup>c</sup> $\delta(^{13}\text{C}) - \delta(^{13}\text{C}$ ref)	Item
		C(5) = 24.3 <sup>k</sup>	27.7	-3.4	39
	R = H	C(6) = 24.9 <sup>h</sup>	29.0	-4.1	40
	R = CH <sub>3</sub>	C(6) = 24.8 <sup>i</sup>	29.0	-4.2	41
Fluorine		C(3,5) = 25.3	28.0	-2.7	42
		C(6) = 22.6 <sup>h</sup>	29.0	-6.4	43
Sulfur		5-CH <sub>3</sub> = 22.5	23.3	-0.8	44
		C(3,5) = 27.6	28.0	-0.4	45
		C(3,5) = 26.5	27.7	-1.2 <sup>m</sup>	46
		C(3,5) = 25.6	27.7	-2.1 <sup>m</sup>	47
		3,5-CH <sub>3</sub> = 23.0	23.4	-0.4	48
		3,5-CH <sub>3</sub> = 21.7	23.4	-1.7	49
		3,5-CH <sub>3</sub> = 21.6	23.4	-1.8	50
Chlorine		C(3,5) = 27.8	28.0	-0.2	51

<sup>a</sup> Chemical shift of italicized or indicated carbon. <sup>b</sup> Resonance of analogous carbon in reference system wherein the heteroatom(s) is (are) replaced by a -CH<sub>2</sub>- or -CH<sub>3</sub> group; see ref 24. <sup>c</sup> Negative values denote upfield shifts. <sup>d</sup> Reference 20. <sup>e</sup> Reference 22. <sup>f</sup> Reference 23. <sup>g</sup> Reference 21. <sup>h</sup> Reference 9. <sup>i</sup> Reference 18. <sup>j</sup> Reference 10. <sup>k</sup> J. B. Stothers, personal communication. <sup>l</sup> Reference 4. <sup>m</sup> Not conformationally homogeneous.

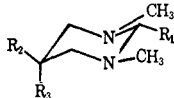
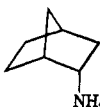
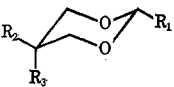
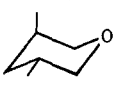

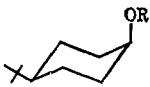
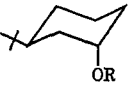
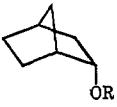
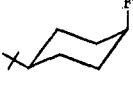
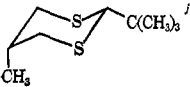
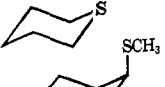


shift of a  $\gamma$  carbon, anti-periplanar chlorine has a negligible effect (*cf.* item 51 and ref 14 and 15). Moreover, a simple calculation of the electrostatic-field effect caused by an anti-periplanar  $\gamma$  oxygen, using either a point dipole or an equivalent charge distribution model to give the overall molecular dipole moment, suggests that the contribution from this source to the upfield shift should amount to less than 0.7 ppm compared with an observed effect for a single oxygen (Table I, items 28, and 31-41) of 2.1-5.9 ppm. A dielectric constant of 2 was assumed for the hydrocarbon-like medium interspersed between the electronegative group and the carbon of interest.

In an effort to explain the upfield shifts of the C(6) resonance in exo-2-heterosubstituted norbornanes (items 15, 40, 41, and 43), Grutzner, *et al.*,<sup>9</sup> have suggested, by analogy with the model used to explain long-range spin-spin coupling through a "W" arrangement of  $\sigma$  bonds,<sup>33</sup> mechanism c involving overlap of the back lobes of the C(2) and C(6) bonding orbitals. A similar explanation has been offered by Anteunis<sup>34</sup> to account for the high field resonance of equatorial 5-protons in 1,3-dioxane and derivatives. While it would be tempting to invoke similar interactions to rationalize the carbon-13 shielding effects of anti-periplanar sec-

ond-row heteroatoms, it is not yet clear to us how such a mechanism could account for the apparent lack of  $\gamma$  shielding by anti-periplanar third-row heteroatoms.

We are led to propose mechanism d as a plausible explanation for the apparently unique role which N, O, and F play in the  $\gamma$  anti shift. Partial  $\pi$ -bond involvement of the free-electron pairs of these second-row elements is favored by the shorter C-X bond and the more nearly similar radial dimension of these atoms with that of carbon. Conversely, Cl and S have larger covalent radii and less favorable radial matching with the  $p\pi$  orbitals of carbon.<sup>35</sup> Figure 3 proposes the nature of the transmission of the electronic effect to the  $\gamma$  position. Coupling-constant data are replete with evidence for the importance of the trans *vs.* cis or gauche structure in 1,4 spin-spin interactions which involve hyperconjugative deviations of the type proposed in Figure 3. The reduced but nonnegligible cis and gauche 1,4-interactions could also provide a qualitative explanation for the enhanced  $\gamma$ -gauche-substituent parameters noted in this study. That a steric upfield shift is also present in the  $\gamma$ -gauche interaction is suggested by methyl proton deshielding in axial 5-methyl substituents in 1,3-dioxanes. The average resonance of an axial 5-CH<sub>3</sub> (1.24 ppm in carbon tetra-

Table II. Shielding Effects (ppm) of Heteroatoms Gauche to Carbon in Representative Molecules

Heteroatom	System	$\delta(^{13}\text{C})$ , <sup>a</sup> ppm from TMS	$\delta(^{13}\text{C ref})$ , <sup>b</sup> ppm from TMS	$\gamma$ effect, <sup>c</sup> $\delta(^{13}\text{C}) - \delta(^{13}\text{C ref})$	Item				
Nitrogen		R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>					
		CH <sub>3</sub>	CH <sub>3</sub>	CH <sub>3</sub>	25.9	25.5	+0.4	52	
		C <sub>2</sub> H <sub>5</sub>	CH <sub>3</sub>	CH <sub>3</sub>	25.7	25.5	+0.2	53	
		CH(CH <sub>3</sub> ) <sub>2</sub>	CH <sub>3</sub>	CH <sub>3</sub>	26.4 <sup>d</sup>	25.5	+0.9	54	
		C(CH <sub>3</sub> ) <sub>3</sub>	CH <sub>3</sub>	CH <sub>3</sub>	28.4–29.2 <sup>d</sup>	25.5	+2.9 to +3.8	55	
Oxygen					C(6) = 20.6 <sup>e</sup>	22.4	-1.8	56	
		R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>					
		CH <sub>3</sub>	H	CH <sub>3</sub>	16.2	19.5	-3.3	57	
		C(CH <sub>3</sub> ) <sub>3</sub>	H	CH <sub>3</sub>	15.9 <sup>f</sup>	19.5	-3.6	58	
		C(CH <sub>3</sub> ) <sub>3</sub>	CH <sub>3</sub>	CH <sub>3</sub>	23.4 <sup>f</sup>	25.5	-2.1	59	
					3,5-CH <sub>3</sub> = 17.6	21.1	-3.6	60	
					C(5) = 24.8 C(7) = 20.3	25.1 21.9	-0.3 -1.6	61 62	
		R = H			C(3,5) = 21.0 <sup>g</sup>	22.6	-1.6	63	
		R = Ac			C(3,5) = 22.1 <sup>g</sup>	22.6	-0.5	64	
		R = H			C(3) = 40.8 <sup>h</sup> C(5) = 20.6 <sup>h</sup>	43.4 22.3	-2.6 -1.7	65 66	
		R = Ac			C(3) = 41.7 <sup>h</sup> C(5) = 21.3 <sup>h</sup>	43.4 22.3	-1.7 -1.0	67 68	
	Fluorine		R = H			C(6) = 20.4 <sup>e</sup>	22.4	-2.0	69
			R = CH <sub>3</sub>			C(6) = 20.5 <sup>i</sup>	22.4	-1.9	70
						C(3,5) = 21.5	22.6	-1.1	71
	Sulfur					5-CH <sub>3</sub> = 16.4	19.5	-3.1	72
					C(4) = 26.5	27.7	-1.2	73	
					C(3,5) = 21.9	22.6	-0.7	74	
Chlorine					C(3,5) = 21.2	22.6	-1.4	75	

<sup>a</sup> See footnote a, Table I. <sup>b</sup> See footnote b, Table I. <sup>c</sup> See footnote c, Table I. <sup>d</sup> Probably in twist-boat conformation, see text. <sup>e</sup> Reference 9. <sup>f</sup> See also ref 18. <sup>g</sup> References 10 and 11. <sup>h</sup> J. B. Stothers, personal communication. <sup>i</sup> Reference 4, p 43. <sup>j</sup> V. S. Rao, personal communication.

chloride)<sup>36</sup> is deshielded by 0.3 ppm relative to the signal of an isolated axial methyl group in cyclohexane (0.94 ppm).<sup>37</sup>

The magnitude of the upfield shift effect seems to decrease as the number of substituents on the shielded carbon increases. Thus, for example, the quaternary carbon of equatorial 5-*tert*-butyl groups in the 1,3-dioxane system are shielded by only -1.4 to -2.3 ppm (items 23-27), while equatorial 5-methyl carbons in this system are much more strongly shielded (items 16-20). This trend, however, is similar to that noted in ethyl, isopropyl, and *tert*-butyl halides.<sup>2</sup> Additional methyls attached to a perturbed carbon appear to exercise a leveling influence on the carbon shift. Whether this is due to the adjacent carbons, their attached hydrogens, or a combination of both is not entirely known. Germane to these observations is the fact that the methyl protons of equatorial 5-methyl-1,3-dioxanes (average resonance, 0.67-0.75 ppm in carbon tetrachloride)<sup>38,39</sup> are found at considerably higher field than the average resonance of an equatorial methyl group in cyclohexane (0.89 ppm).<sup>6,37</sup> Furthermore, it has been noted that both an equatorial 5-proton<sup>34,38,39</sup> and an equatorial 5-fluorine<sup>40</sup> are strongly shielded in the 1,3-dioxane system, and, contrary to the trends found for cyclohexane and derivatives, these nuclei resonate at higher field than their axial counterparts.

The fact that the efficacy of  $\gamma$  anti shielding by nitrogen (items 1, 3, 5, 7-13, and 15) is enhanced upon protonation (items 2, 4, 6, and 14) and the analogous shielding observed in passing from sulfides (items 46, 48) to the corresponding sulfonium salts (items 47, 49, 50) requires a different explanation and suggests that the electron density changes at the heteroatom in the ammonium or sulfonium ion does influence the effective nuclear charge at distant carbon atoms. The best explanation<sup>23,41</sup> for such a shift appears to be either a  $\sigma$ -inductive effect<sup>41a</sup> or an electrostatic-field effect.<sup>41b</sup> It may be argued further that the mono-pole unit charge associated with protonation will be a much stronger perturbation than that due to the dipole moments associated with N, O, and F, and therefore, dipole-induced  $\sigma$  polarization and/or electrostatic field effects could only account for a small part of the  $\sigma$  anti shift in the unprotonated compounds.

**Structural Assignments.** The majority of compounds used in this study were prepared by standard techniques; configurational assignments for the piperidines,<sup>29,42</sup> 1,3-diazanes,<sup>29,30,43</sup> 1,3-dioxanes,<sup>38,44</sup> 1,3-dithianes,<sup>45</sup> thianium salts,<sup>46</sup> and 4-*tert*-butylcyclohexyl halides<sup>47</sup> and sulfides<sup>48</sup> have been previously made by a variety of physical and chemical methods.

The synthesis of *trans*-1,3-dioxadecalin<sup>49</sup> from cyclohexene and aqueous formaldehyde by a modified Prins reaction and the preparation of *cis*-1,3-dioxadecalin from *cis*-2-hydroxymethylcyclohexanol<sup>50</sup> served to establish the configuration of these compounds. Of the two possible preferred conformations of *cis*-1,3-dioxadecalin shown in Figure 4, A should be favored over B on energetic grounds since an axial substituent at the C(5) position of the dioxane ring [C(10) in the dioxadecalin system] has a much smaller conformational energy than an axial substituent at C(4) in the dioxane ring<sup>38</sup> [C(9) in the dioxadecalin system]. This same conclusion is reached if the dioxadecalin is viewed as a substituted cyclohexane since conformation A has axial O (0.4 kcal/mol)<sup>51</sup> whereas B has axial -CH<sub>2</sub>- (ca. 1.7 kcal/mol).<sup>52</sup> This assignment is supported by the pmr spectrum which shows a completely degenerate H(4) pattern, as expected<sup>53</sup> of conformation A but not of conformation B which should give an H(4) signal similar to that found for *trans*-1,3-dioxadecalin (*cf.* Experimental Section).

Configurational assignments of *cis*- and *trans*-3,5-di-

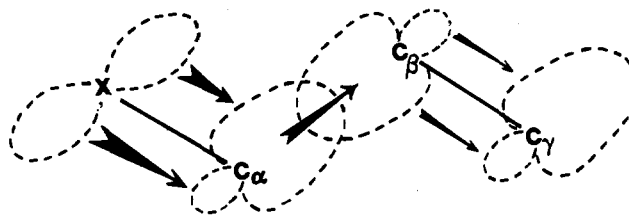


Figure 3. Hyperconjugative transfer of charge from free-electron pairs on X atom to *trans*  $\gamma$  carbon. (This mechanism will be enhanced by coplanarity of the p-orbital contribution in the four atomic orbitals indicated.)

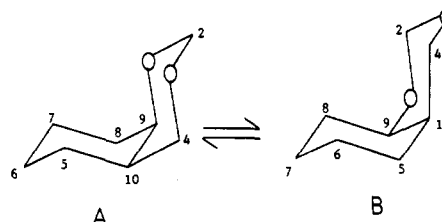


Figure 4. *cis*-1,3-Dioxadecalin.

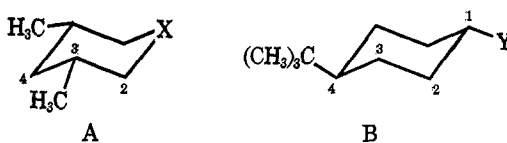
methyltetrahydropyran were based on an analysis of the pmr spectrum of a mixture of these isomers. The major component (85%) was assigned the *trans* configuration since the H(2) and H(6) signals appear as the expected AA'BB' portion of an AA'BB'XX' pattern with averaged couplings such that:  $J_{AB} = -11.0$ ,  $J_{AX} = \frac{1}{2}(J_{ee} + J_{aa}) = 6.0$ , and  $J_{BX} = \frac{1}{2}(J_{ae} + J_{ea}) = 3.6$  Hz. The averaged methyl resonance at 0.93 ppm is consistent with this assignment, whereas the rather high field (0.79 ppm) doublet could only be assigned to the *cis*-3,5-dimethyl isomer. In the *cis* isomer, the axial H(2,6) signal would be expected to show two large couplings,  $^3J_{aa}$  and  $^2J$ . Fortunately, these couplings are of equal absolute magnitude (11.0 Hz), and the axial H(2,6) resonance appears as an apparent triplet at 2.85 ppm.

**Shifts at Other Positions.** In Table 4 (microform appendix)<sup>54</sup> are given the chemical shifts of all carbons in the compounds first reported in this paper (items 4, 9-14, 16-18, 21, 22, 28, 29/30, 33, 34/35, 36/37, 38/39, 42, 44-55, 57, 60, 61/62, 65/66, 67/68, and 70-75). The assignments, in most cases, are straightforward. Detailed interpretation of all the data is not within the purview of this paper, but two sets of homologous compounds (Chart I) warrant brief consideration.

The data in Chart I, B, indicate a consistent upfield shift of 1-2 ppm by a hetero substituent compared with methyl. Unlike the  $\gamma$  shifts, the  $\delta$  shifts correlate neither with electronegativity nor with whether the heteroatom is in the second or third row of the periodic system. The  $\delta$  shifts have been recognized and their possible origin speculated upon before.<sup>11</sup>

Little can be said about  $\alpha$  and  $\beta$  shifts. The  $\alpha$  shifts caused by hetero substituents are generally downfield, as previously observed in the case of alcohols<sup>11</sup> and amines.<sup>15</sup> However, whereas previously observed<sup>11,15</sup>  $\beta$  shifts were also downfield, in the present case both upfield and downfield shifts were observed, with the former predominating, especially for O, N (neutral), and F. Perhaps it is best to leave this matter with a citation from a previous paper:<sup>11</sup> "The problem in sorting out these influences . . . is that with many substitutions a composite of effects is to be expected. It might be expected that one could assume that the inductive and steric effects dominate at the  $\alpha$ - and  $\beta$ -carbons while the steric effects dominate at the carbons farther

Chart I. Chemical Shifts (ppm) from TMS



Compound A				
X	CH <sub>2</sub>	O	NH	S
C(2)	35.6	74.1	49.8	35.3
C(3)	33.0	31.5	28.4	34.4
C(4)	44.9	41.9	40.2	44.0
CH <sub>3</sub>	23.0	17.5	18.8	23.0

Compound B								
Y	CH <sub>3</sub> <sup>a</sup>	F	OH <sup>b</sup>	OCH <sub>3</sub>	NH <sub>2</sub>	NH <sub>3</sub> <sup>+</sup>	SCH <sub>3</sub>	Cl
C(1)	32.8	91.5	70.4	79.8	51.0	51.6	44.8	59.4
C(2)	36.7	33.5	35.7	32.2	37.4	31.5	33.7	38.1
C(3)	28.2	25.3	21.0	25.6	26.3	25.7	27.6	27.8
C(4)	49.2	47.3	48.2	47.5	47.6	46.8	47.5	47.2

<sup>a</sup> See footnote 24. <sup>b</sup> References 10 and 11.

from the point of substitution. While the latter assumption is likely to be valid, the former is probably too naive . . . .” We subscribe to this statement as far as  $\alpha$  and  $\beta$  effects are concerned, although, as the present study has shown, its applicability at the farther sites, such as C <sub>$\gamma$</sub> , is put in question.

### Experimental Section

Carbon-13 spectra of chloroform solutions of the piperidines and 1,3-diazanes were recorded on a previously described<sup>55</sup> Fourier transform spectrometer operating at 15.08 MHz. The solvent signal was used as internal standard, and the shifts were converted to the TMS scale using  $\delta(\text{C}^{\text{CHCl}_3}) = 77.2$  ppm. The remaining samples were preferentially dissolved in a minimum of carbon disulfide containing TMS as internal standard, and the spectra were recorded on either a Varian XL-100-15, a Varian AFS-60, or a Bruker Scientific HFX-8 spectrometer as previously described.<sup>18</sup> Assignments were made by selective proton decoupling<sup>56</sup> of an assigned proton from a given carbon resonance in those instances where an assignment could not be made on the basis of relative intensities or the observed proton induced splittings in the off-resonance decoupled spectrum.

**Compound Preparation.**<sup>57</sup> With the exceptions of the following compounds, the samples used in this study were either available from previous studies<sup>30,38,43-47</sup> or were synthesized by previously described methods.<sup>42-47</sup>

**trans-1,3-Dioxadecalin.**<sup>49</sup> One mole (102.0 ml, 82.15 g) of cyclohexene was added at once to a stirred solution of 17 ml of concentrated sulfuric acid in 300 ml of aqueous (37.4%) formaldehyde. The brownish mixture was heated with stirring at 70° overnight. After the mixture was cooled to room temperature, the organic phase was separated (aqueous phase discarded) and was washed successively with 50 ml of 10% sodium bicarbonate, 50 ml

of 20% sodium bisulfite, and 50 ml of water. Benzene (100 ml) was added to the organic phase, and the volatile components were removed by rotary evaporation (at ca. 20 mm). The pale yellow residue was distilled through a short Vigreux column to give 115.9 g (82%) of product, bp 78–82° (15mm) [lit.<sup>49</sup> 90–93° (30 mm)]. An analytical sample for carbon-13 study was obtained by preparative glc on a 6-ft column packed with 20% FFAP on Chromosorb W (45–60 mesh) at 117°:  $n_D^{20}$  1.4661 (lit.<sup>49</sup>  $n_D^{25}$  1.4632); ir (neat) 1378 (s), 1160 (vs), 1095 (s), 1082 (vs), 1060 (s), 1030 (vs), 1010 (vs), 968 (s), 920 (s), and 687 (s) cm<sup>-1</sup>; pmr (CCl<sub>4</sub>)  $\delta$  0.60–1.90 (broad, 9 H), 3.18 (m, 2 H), 3.80 (dd,  $J = 10.90$ ,  $J = 4.15$  Hz, 1 H), 4.61 and 4.87 ppm (AB,  $J_{AB} = 6.20$  Hz, 2 H). *Anal.* Calcd for C<sub>8</sub>H<sub>14</sub>O<sub>2</sub>: C, 67.57; H, 9.92. Found: C, 67.77; H, 9.99.

**cis-1,3-Dioxadecalin.** A solution of 6.5 g (0.050 mol) of *cis*-2-hydroxymethylcyclohexanol,<sup>50</sup> 1.52 g of paraformaldehyde, and a catalytic quantity of *p*-toluenesulfonic acid monohydrate in 25 ml of benzene was stirred at room temperature for 8 hr. The reaction flask was then equipped with a Dean-Stark trap and reflux condenser, and the solution was refluxed until 1.0 ml of water had collected. The product mixture was cooled to room temperature and stirred for 40 min with 0.5 g of anhydrous potassium carbonate. The mixture was then filtered, the solid washed with benzene, and the solvent removed at reduced pressure (ca. 20 mm). The residue was distilled to give 3.84 g (54%) of mixed 1,3-dioxadecalins, bp 74–75° (14 mm) (86.6% *cis* and 13.4% *trans*). Purification of the *cis* isomer was accomplished by preparative glc on a 6-ft column packed with 20% FFAP on Chromosorb W (45–60 mesh) at 120°: ir (neat) 1183 (s), 1152 (s), 1111 (s), 1053 (s), 1015 (s), 970 (s), and 928 (s) cm<sup>-1</sup>; pmr (CCl<sub>4</sub>)  $\delta$  1.00–2.25 (broad, 9 H), 3.68 (m, 3 H), 4.55 and 4.90 ppm (AB,  $J_{AB} = 6.20$  Hz, 2 H). *Anal.* Calcd for C<sub>8</sub>H<sub>14</sub>O<sub>2</sub>: C, 67.57; H, 9.92. Found: C, 67.67; H, 10.03.

**cis- and trans-3,5-Dimethyltetrahydropyran.** A solution of 14 g (0.074 mol) *p*-toluenesulfonyl chloride in 10 ml of pyridine was

Table III. Yields and Properties of 2-Substituted *N,N'*-5,5-Tetramethyl-1,3-diazanes

R	Yield, %	Bp, °C (mm)	Analysis			
			Calcd		Found	
			C	H	C	H
CH <sub>3</sub>	67	50 (2)	69.17	12.90	68.91	12.78
C <sub>2</sub> H <sub>5</sub>	38	70 (8)	70.53	13.02	70.66	12.95
CH(CH <sub>3</sub> ) <sub>2</sub>	61	70 (52)	<sup>a</sup>	<sup>a</sup>	<sup>b</sup>	<sup>b</sup>
C(CH <sub>3</sub> ) <sub>3</sub>	56	34 (7)	72.66	13.21	72.89	12.98

<sup>a</sup> Calcd for C<sub>11</sub>H<sub>24</sub>N<sub>2</sub>, *m/e* 184.1939. <sup>b</sup> Found, *m/e* 184.1937.

added dropwise to a stirred refluxing solution of 6.6 g (0.050 mol) of mixed *meso*- and *dl*-2,4-dimethyl-1,5-pentanediol<sup>58</sup> in 10 ml of pyridine. After being heated at reflux for an additional 1.5 hr, the solution was cooled to room temperature and poured over a 50% (wt/wt) mixture of ice-concentrated sulfuric acid. The mixture was extracted with three 100-ml portions of ether, and the combined ethereal extracts were dried over anhydrous magnesium sulfate. Distillation of the dried extract through a short Vigreux column afforded 2.55 g (45%) of 3,5-dimethyltetrahydropyrans, bp 140–160°. Since it was not possible to separate the isomeric products chromatographically, the carbon-13 spectrum was obtained from an analytically pure sample of mixed isomers. The pmr spectrum (discussed above) indicated a mixture composed of 85% *trans*- and 15% *cis*-3,5-dimethyltetrahydropyran. *Anal.* Calcd for C<sub>7</sub>H<sub>14</sub>O: C, 73.63; H, 12.36. Found: C, 73.46; H, 12.41.

**2-Substituted-*N,N',5,5*-Tetramethyl-1,3-diazanes.** An equimolar amount of the appropriate aldehyde was slowly added to *N,N',2,2*-tetramethyl-1,3-propanediamine<sup>59</sup> contained in a round-bottom flask fitted with a magnetic stirrer and a reflux condenser. After the mixture was stirred an additional 10 min, a Dean-Stark trap was inserted between the flask and condenser, and dry benzene (typically, 15–25 ml for a 0.01-mol run) containing a catalytic quantity of *p*-toluenesulfonic acid monohydrate was added to the flask. The reaction mixture was refluxed until the theoretical amount of water had collected in the trap, the residual benzene removed by rotary evaporation (at *ca.* 20 mm), and the residue distilled. Yields and properties of products are listed in Table III.

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**Supplementary Material Available.** A table of cmr chemical shifts for all carbons in all new compounds will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D.C. 20036. Remit check or money order for \$3.00 for photocopy or \$2.00 for microfiche, referring to code number JACS-75-322.

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## Gd(fod)<sub>3</sub>-Induced Contact Shifts. A Versatile New Method to Estimate Contact and Pseudocontact Shift Contributions to Observed Lanthanide-Induced Shifts

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**Abstract:** A new method to separate the lanthanide-induced shifts into contact, pseudocontact, and complex formation contributions is described. We propose that the Gd(fod)<sub>3</sub>-induced <sup>13</sup>C shifts are a versatile measure of the contact contributions for shifts induced by lanthanide shift reagents other than Gd(fod)<sub>3</sub>. We also suggest that shifts due to the complex formation between shift reagents and substrates should be quite small in cases of aliphatic compounds. On the other hand, in cases of aromatic compounds, the complex formation shifts were found to be significant. The interpretation is strongly supported by comparison of the evaluated contact shifts and pseudocontact shifts with theoretical values.

Chemical shifts induced by lanthanide shift reagents have been assumed to be dominated by the pseudocontact interaction. This assumption has been supported by the well-documented facts that for <sup>1</sup>H nmr the observed shifts nicely coincide with the calculated values based upon the simple axially symmetric pseudocontact equation.<sup>1-3</sup> However, recent observations of many anomalous lanthanide-induced shifts, mainly for other nuclei than <sup>1</sup>H, cannot easily be explained by pseudocontact shifts. This questions the assumption concerning the origin of the induced shifts for these nuclei.<sup>3-8</sup>

These abnormal shifts might be caused partly by contact interaction and partly by complex formation between lanthanide chelate and substrate<sup>9</sup> since the induced shifts may contain three contributions, *i.e.*, pseudocontact shifts (PCS), contact shifts (CS), and complex formation shifts (CFS). We have previously indicated that caution must be exercised in the application of lanthanide shift reagents, because the CFS term as well as the CS term are sometimes too large to be ignored in the lanthanide-induced shifts.<sup>10,11</sup> As it seems to be quite essential to have a better knowledge about the relative values of these terms when applying shift reagents to structural analysis, we describe here a new experimental method to separate the lanthanide-induced shifts into the three terms.

### Results and Discussion

Several attempts to estimate the <sup>13</sup>C CS contribution

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quantitatively have been reported so far. Among them, the procedure by Gansow, *et al.*, seems to be worth mentioning.<sup>6</sup> Assuming the lanthanide-induced shifts in <sup>1</sup>H resonance to be almost entirely composed of PCS, they deduced the best fit for the geometry of the lanthanide metal-substrate adduct, with which they in turn calculated the possible <sup>13</sup>C PCS values. The CS contributions to the observed shifts were readily estimated by comparing the calculated PCS with the observed <sup>13</sup>C shifts. It is not necessarily valid, however, that the differences of these two values represent the CS contribution only.

**Estimation of the CFS Term.** As the first step to explain the curious aspects of the shifts induced in <sup>13</sup>C resonances by complexes, we decided to eliminate the CFS contribution from the observed shifts. Such correction can be made using the shift values (*S* values)<sup>12</sup> induced by diamagnetic La(fod)<sub>3</sub> or Lu(fod)<sub>3</sub><sup>13</sup> assuming that the CFS terms are the same for all the other lanthanide shift reagents. This assumption might be reasonable, because the CFS induced by La(fod)<sub>3</sub>, the lightest lanthanide, and by Lu(fod)<sub>3</sub>, the heaviest lanthanide, are usually very similar.<sup>10</sup> In previous work, CFS terms as high as 10 ppm for pyridine *N*-oxide and related aromatic compounds were found.<sup>10</sup> In contrast, for aliphatic compounds, as can be seen in Table I, La(fod)<sub>3</sub>- and Lu(fod)<sub>3</sub>-induced shifts are quite small, so it might be concluded that the CFS is not a major contribution to the abnormality of the <sup>13</sup>C lanthanide shifts for these compounds.

**Gd(fod)<sub>3</sub> Induced Shifts as a Measure of the CS Term.** Previous reports have suggested the Gd complexes as useful