

Intramolecular van der Waals' Interactions and
 ^1H Chemical Shifts: Steric Effects in Some Cyclic Systems

by

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Abstract - In previous studies it was found that linear correlations existed between the local van der Waals' interaction energies calculated by the MM2 force field and chemical shifts of the resonant nuclei for ^{13}C , ^{15}N , and ^{31}P in saturated acyclic and cyclic systems. This paper extends these studies to the protons in some cyclic systems. A total of 45 carbinol protons in substituted cyclohexanols and decalols, 19 methylene protons and 7 methine protons in substituted cyclohexanes and decalins were analyzed. Similar correlations are found with root-mean-square errors of 0.19, 0.20 and 0.07 ppm. Most of the steric effects on chemical shifts of protons are well interpreted by this model.

Introduction

While the results of steric effects on the chemical shifts of protons were studied by magnetic anisotropic theory many years ago^[1-3], there remain some major inconsistencies between the predictions and observations.^[4-5] The intramolecular van der Waals' effects on the chemical shifts of protons were considered only qualitatively, or only for some special cases (such as Cheney's equation)^[6], and usually only the dispersion force was considered.^[7] Tribble^[8] used van der Waals' dispersion combined with magnetic anisotropic to calculate the chemical shifts of protons in hydrocarbons, but the unusual upfield shift of equatorial protons between two equatorial methyl groups in disubstituted cyclohexanes remained unexplained. We treated the data in Table II of Tribble's paper with multiple regression. The t_p values for V, W, X, Y, Z are 0.24, 0.83, 1.18, 1.40, -0.70, respectively. For this data set (18 data, 13 degrees of freedom) the $t_{90\%}$ is 1.35, $t_{95\%}$ is 1.77, $t_{99\%}$ is 2.65. Therefore, if only one of them is considered, it cannot be linearly related to the chemical shifts. In the present work we used both the attractive and the repulsive parts of the van der Waals' interaction to study steric effects on chemical shifts in a new way, and we obtained results almost as good as Tribble did (he used 5 adjustable parameters). Most of the unusual behavior of proton chemical shifts which could not be understood by magnetic anisotropic theory can be well interpreted by our model.

Recently we studied the steric effects of substituents on the chemical shifts of ^{13}C , ^{15}N , and ^{31}P by molecular mechanics calculations^[9]. It was found that the steric effects of substituents on the chemical shift of a heavy atom are mainly controlled by the local van der Waals' interactions. The shielding and deshielding effects are related to the attractive and repulsive parts of the van der Waals' interaction, respectively. Using this model, not only is the γ -shielding effect well explained, but also the large β -deshielding, and the δ , ϵ ,... effects can be well understood.^[10]

The long-range nuclear magnetic shielding of protons was explained by diamagnetic bond-anisotropy theory which was proposed and treated by Bothner-By and Near-Colin^[1], McConnel^[2] and Musher.^[3] The chemical shifts of 21 different substituted cyclohexanols were interpreted in terms of carbon-carbon bond anisotropy with appropriate parameters^[3]. But Eliel^[4] and Muller^[5] found evidence of inconsistencies between the observations and calculations by Musher's method.

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Cheney^[6] put forward equation 1 to explain the steric effect on chemical shifts of protons from van der Waals' interaction^[6], but only for some special cases.

$$\delta_S^H = -105 \int \cos \theta_i \exp(-2.671\gamma_i) \quad (1)$$

where γ_i is the distance between protons H and H_i , and θ_i is the angle between the extension of the vector γ_i and the C-H bond.

In 1970 Tribble, Miller and Allinger^[8] combined a magnetic anisotropic equation with Zurcher's van der Waals' equation^[7] to give a semi-empirical equation (2), including 5 adjustable parameters, which was used to calculate the chemical shifts of protons in hydrocarbons:

$$\delta_H = V\chi_{L-C-C} + W\chi_{T-C-C} + X\chi_{L-C-H} + Y\chi_{T-C-H} + ZB \quad (2)$$

where V, W, X, Y, and Z are the geometrical factors associated with χ_{C-C} , χ_{T-C-C} , χ_{C-H} , χ_{T-C-H} and B. χ_L is the magnetic susceptibility of the bond along its symmetry axis, χ_T is the magnetic susceptibility of the bond along the direction normal to the symmetry axis. B is the dispersion constant.

Their results showed that in many cases the van der Waals' interaction was more important than the magnetic anisotropic effect. However, the different kinds of protons (such as methyl, methylene, and methine protons) were not distinguished in their paper. The differences between the chemical shifts of different kinds of protons were considered to result only from the anisotropic and van der Waals' effects. As a matter of fact, the change from a C-H bond to a C-C bond will cause an apparent inductive effect on the hydrogens attached on this carbon. On the other hand, Zurcher's van der Waals' equation only considered the van der Waals' dispersion force (i.e. attraction). In fact, some of the atoms in a typical molecule are so close to one another that they are located in the repulsive region of van der Waals' interaction. In general, the repulsive and attractive parts of van der Waals' interactions should have different influences on the chemical shifts of resonant nuclei.

In this work the relationships between steric effects and chemical shifts of protons were studied by molecular mechanics calculations, and it was found that the local van der Waals' interactions are the main factor governing the steric effect on the chemical shift of a proton. There exist good linear relationships between the local van der Waals' interaction energies (E_{VDW}) and chemical shifts (δ_H).

Calculations

The MM2 force field^[11] was used in this work, and the program was the 1980 version^[12]. The compounds we selected for study include substituted cyclohexanes, cyclohexanols, decalins and decalols.

All of the calculations of chemical shifts use equation 3,

$$\delta_i = b + c_{VDW} E_{VDW,i} \quad (3)$$

The reference compound for proton chemical shifts is tetramethylsilane (TMS). A positive value of δ means a shift downfield from the TMS protons.

The hydrogens on different kinds of carbons have different bases, but the hydrogens on the same kind of carbons usually have the same base, except where crowding leads to severe angular deformations. Altogether, three kinds of hydrogens were studied: the hydrogens on secondary carbons (methylene hydrogens), the hydrogens on tertiary carbons (methine hydrogen) and carbinol hydrogens. The constants b and c in eq. 3 were evaluated from experimental data for the three separate classes of protons.

Since the chemical shift is related only to the resonant nucleus and its environment, we looked specifically at the local van der Waals' interaction energies of the resonant protons as the

first approximate measurement of the steric effects. Our previous results^[9] showed that although the other components of the steric energies made definite contributions to the chemical shifts, for the same kinds of resonant nuclei, these changes were small except in congested or highly strained systems, and they did not have as simple a correlation with the chemical shifts as the van der Waals' energies did.

The rotation of a hydroxyl group will produce three conformations. The rotation of ethyl and isopropyl groups also will produce additional conformations. There are two ways to deal with different conformations. One is to compare the E_{VDW} for only the lowest steric energy conformation. The other, more proper, way is to use the Boltzmann averaged E_{VDW} values.

It was found that for 41 cyclic alcohols the results from these two methods are very similar (see Table 1). Therefore, in order to simplify the treatment, only the lowest steric energy conformation was used except for compound 26 (cis-2-ethylcyclohexanol), which has several conformations of very similar steric energies but of quite different E_{VDW} .

Table 1* Comparison of Chemical Shifts (δ) for the Lowest Energy Conformation ($E_{VDW L}$) and the Boltzmann Averaged Conformations ($E_{VDW A}$) for 41 Compounds (Table 2)

	$E_{VDW L}$	$E_{VDW A}$
Correlation coefficient (r)	0.848	0.853
Constant c_{VDW}	2.375	2.365
Constant b	1.537	1.558
RMS error (ppm)	0.193	0.190

*Energy in kcal/mol.

Results and Discussion

In this paper we specifically look at the chemical shifts of protons in cyclic systems, especially in cyclohexanes and cyclohexanols. In these systems, some of the chemical shifts of protons show unusual behavior^[5]. We have analyzed 45 carbinol protons in cyclic alcohols, and the results are listed in Table 2. The general linear relationship between E_{VDW} and δ_H for these compounds is shown in Fig. 1. For cis-2-t-butylcyclohexanol, cis-2-isopropylcyclohexanol, neomenthol, and neoisomenthol, the E_{VDW} values were overestimated very much when only the lowest steric energy conformations were considered. But if the conformation in which one of the methyl groups of the isopropyl is axial to the hydroxyl group was selected, then the E_{VDW} for the last three compounds became normal and their points are near the regression line (which is shown in Fig. 1 as dashed circles). However, these conformations have steric energies about 1 kcal/mol higher than the minimum energy conformations, therefore, these four points were not used in the regression analysis.

For substituted cyclohexane systems, due to their complicated spectra, the chemical shifts of hydrogens were determined directly for only a few compounds^[13]. But Booth^[14] developed an empirical rule for substituent effects on the chemical shifts of protons in cyclohexanes. According to Booth's data plus a few additional experimental data, 19 resonant methylene protons and 7 resonant methine protons were analyzed. These results are given in Tables 3 and 4, respectively. The linear relations between E_{VDW} and δ_H are shown in Fig. 2 and 3.

From Tables 2-4 and Figs. 1-3 it is clear that the general relationship between the E_{VDW} and δ_H is reasonably good. The results of regression analyses are listed in Table 5.

Table 2. Chemical Shifts and E_{VDW} of Carbinol Protons in Cyclohexanols

R-cyclohexanol	δ_{obs}	E_{VDW}	δ_{calc}	$\Delta\delta(obs-calc)$
1 <u>trans-4-t-butyl</u>	3.37	0.7125	3.23	0.14
2 <u>cis-4-t-butyl</u>	3.93	0.9338	3.76	0.17
3 <u>trans-3-t-butyl</u>	4.07	0.9990	3.91	0.16
4 <u>cis-3-t-butyl</u>	3.43	0.7382	3.29	0.14
5 <u>trans-2-t-butyl</u>	3.40	0.9108	3.70	-0.30
6 <u>cis-2-t-butyl</u>	4.16	1.4814		
7 <u>menthol</u>	3.27	0.8720	3.61	-0.34
8 <u>neomenthol</u>	4.02	1.4337		
9 <u>trans-4-methyl</u>	3.38	0.7320	3.28	0.10
10 <u>cis-4-methyl</u>	3.88	0.9480	3.79	0.09
11 <u>cis-3-methyl</u>	3.45	0.7444	3.31	0.14
12 <u>trans-3-methyl</u>	3.97	0.9564	3.81	0.16
13 <u>trans-2-methyl</u>	2.98	0.6349	3.05	-0.07
14 <u>cis-2-methyl</u>	3.75	0.8758	3.62	0.13
15 <u>cis-3,3,5-trimethyl</u>	3.65	0.8856	3.64	0.01
16 <u>trans-3,3,5-trimethyl</u>	4.10	1.1014	4.15	-0.05
17 <u>trans-2-isopropyl</u>	3.25	0.8712	3.61	-0.36
18 <u>cis-2-isopropyl</u>	4.00	1.4334		
19 <u>trans-2-trans-6-dimethyl</u>	2.42	0.5090	2.75	-0.33
20 <u>cis-2-cis-6-dimethyl</u>	3.47	0.7922	3.42	0.05
21 <u>3,3,5,5-tetramethyl</u>	3.82	0.9787	3.86	-0.04
22 <u>3,3-dimethyl</u>	3.65	0.8945	3.66	0.01
23 <u>trans-2-ethyl</u>	3.08	0.6399	3.06	0.02
24 <u>cis-2-ethyl</u>	3.81	1.0045	3.92	-0.11
25 <u>cis-2-trans-6-dimethyl</u>	3.22	0.8007	3.44	-0.22
26 <u>trans-2-methyl-trans-4-t-butyl</u>	2.93	0.5985	2.96	-0.03
27 <u>trans-2-methyl-cis-4-t-butyl</u>	3.57	0.8931	3.66	-0.09
28 <u>cis-2-methyl-trans-4-t-butyl</u>	3.57	0.8823	3.63	-0.06
29 <u>cis-2-methyl-cis-4-t-butyl</u>	3.67	0.8598	3.58	0.09
30 <u>2,3-dimethyl-trans-4-t-butyl</u>	3.12	0.8457	3.55	-0.43
31 <u>2,2-dimethyl-cis-4-t-butyl</u>	3.31	0.7830	3.40	-0.09
32 <u>2,2-dimethyl</u>	3.20	0.8729	3.61	-0.41
33 <u>cis-3-cis-5-dimethyl</u>	3.48	0.7362	3.29	0.19
34 <u>trans-3-trans-5-dimethyl</u>	4.02	0.9574	3.81	0.21
35 <u>trans-4-isopropyl</u>	3.48	0.7061	3.21	0.27
36 <u>cis-4-isopropyl</u>	(3.99)	0.9400	3.77	0.22
37 <u>trans-2-trans-5-dimethyl</u>	(3.48)	0.7237	3.26	0.22
38 <u>cis-2-trans-5-dimethyl</u>	(3.78)	0.8767	3.62	0.16
39 <u>trans-2-cis-5-dimethyl</u>	(3.02)	0.6260	3.02	-0.00
40 <u>cis-2-cis-5-dimethyl</u>	(3.73)	0.9061	3.69	0.04
41 <u>isomenthol</u>	(3.75)	1.0004	3.91	-0.16
42 <u>neoisomenthol</u>	(4.04)	1.4910		
43 <u>cyclohexanol</u>	(3.50)	0.7483	3.32	0.18
44 <u>trans-10-methyl-trans-decal-2-ol</u>	(3.95)	0.9277	3.74	0.21
45 <u>cis-10-methyl-trans-decal-2-ol</u>	(3.41)	0.8022	3.44	-0.03

*The values in parentheses were taken from ref. 5, the others from ref. 6.

In most cases $\Delta\delta(\delta_{obs} - \delta_{calc})$ is about ± 0.2 ppm or less. Therefore, it can be concluded that the steric effect of substituents on chemical shifts of protons is mainly governed by the local steric van der Waals' interaction energy of the resonant protons, with the repulsive van der Waals' interaction causing a deshielding effect (downfield) and the attractive van der Waals' interaction causing a shielding effect (upfield).

The substituents can change the van der Waals' interaction energy of a resonant proton in two ways. One is that the new addition adds additional van der Waals' interaction energies between the atoms of the substituents and the resonant proton. The other is that the substituents will change the conformation or the relative position of atoms in the molecule, which in turn changes the van der Waals' interaction energy of a resonant proton. Table 6 gives some typical examples to show how the substituents influence the van der Waals' interaction energy of carbinol protons. The numbering systems are shown in Fig. 4. Cyclohexanol is taken as a reference compound (the hydroxyl is equatorial): carbons 3, 5, hydrogens 9, 12, 16, 17, and hydroxyl hydrogen 19 and one of the lone pairs 21 are located in the repulsive van der Waals' interaction region of the carbinol proton. If a substituent such as a t-butyl group replaces hydrogen 13 on carbon 4, it does not change the whole structure or the relative positions of the atoms very much, but all of the atoms in the t-butyl group are located in the attractive van der Waals' interaction region of the carbinol proton. The total result is to increase the attractive van der Waals' interaction energy,

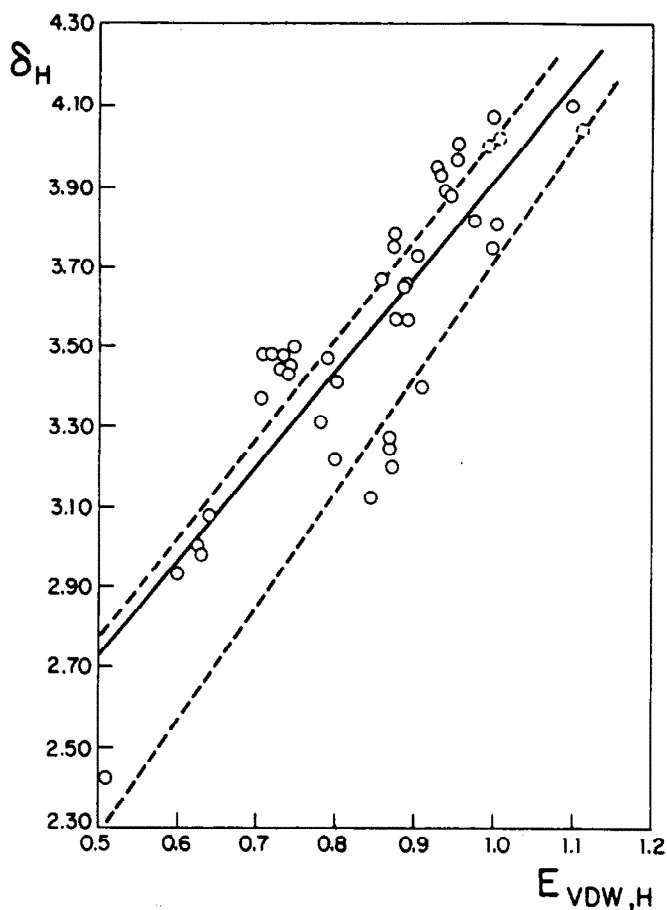


Fig. 1. Observed chemical shift (δ) of carbinol protons vs. local van der Waals' energy in cyclohexanols (compounds.....).

Table 3. Chemical Shifts and E_{VDW} of Methylene Protons in Cyclohexanes

Compound	Position of H	δ_{obs}	E_{VDW}	δ_{calc}	$\Delta\delta(obs-calc)$
cyclohexane	H(2a)	1.17	0.3786	1.25	-0.08
	H(2e)	1.65	0.5035	1.72	-0.07
1-CH ₃ (e)-cyclohexane	H(2a)	0.87	0.2808	0.90	-0.03
	H(2e)	1.68	0.4356	1.46	0.22
	H(3a)	1.20	0.3735	1.24	-0.04
	H(3e)	1.72	0.5010	1.70	0.02
	H(4a)	1.10	0.3653	1.21	-0.11
	H(4e)	1.67	0.4999	1.70	-0.03
1-CH ₃ (a)-cyclohexane	H(2a)	1.37*	0.4796	1.62	-0.25
	H(2e)	1.25*	0.4204	1.41	-0.16
	H(3a)	1.42*	0.4384	1.47	-0.05
	H(3e)	1.73*	0.5161	1.76	-0.03
<u>cis</u> -1,3-di-Me-cyclohexane	H(2a)	0.37*	0.1726	0.50	-0.13
<u>cis,cis</u> -1,3,5-tri-Me-cyclohexane	H(2a)	0.47	0.1715	0.50	-0.03
	H(2e)	1.64	0.3689	1.23	0.42
<u>cis,trans</u> -1,3,5-tri-Me-cyclohexane	H(2a)	1.01	0.3787	1.26	-0.25
	H(2e)	1.52	0.3500	1.15	0.37
	H(4a)	0.47	0.1931	0.58	-0.11
	H(4e)	1.52	0.3610	1.19	0.33

* These data are calculated from Booth's empirical rules (ref. 13). The others are experimental data (ref. 9b, 12, 13). Chemical shifts are in ppm. E_{VDW} are in kcal/mol.

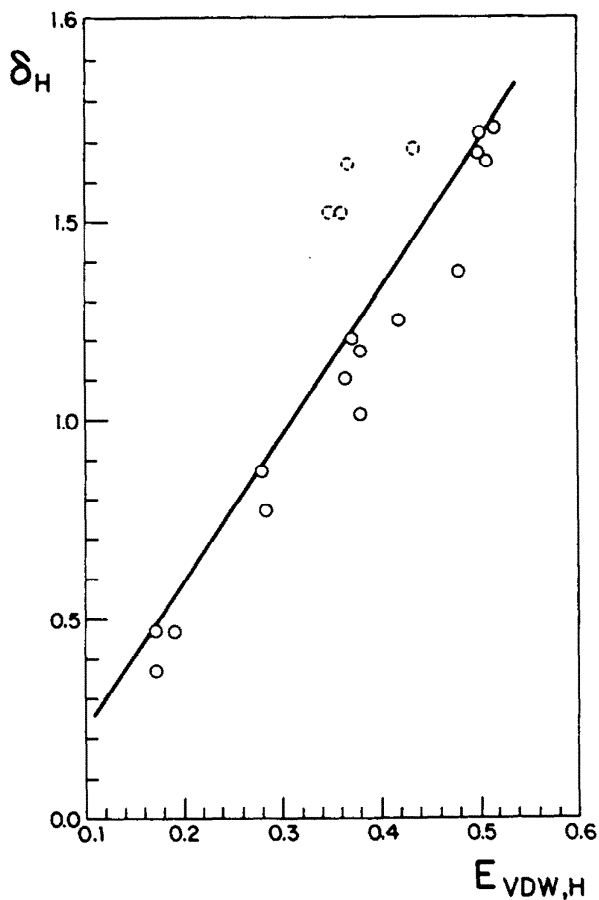


Fig. 2. Observed chemical shift (δ) of methylene protons vs. local van der Waals' energy in cyclohexanes (compounds.....).

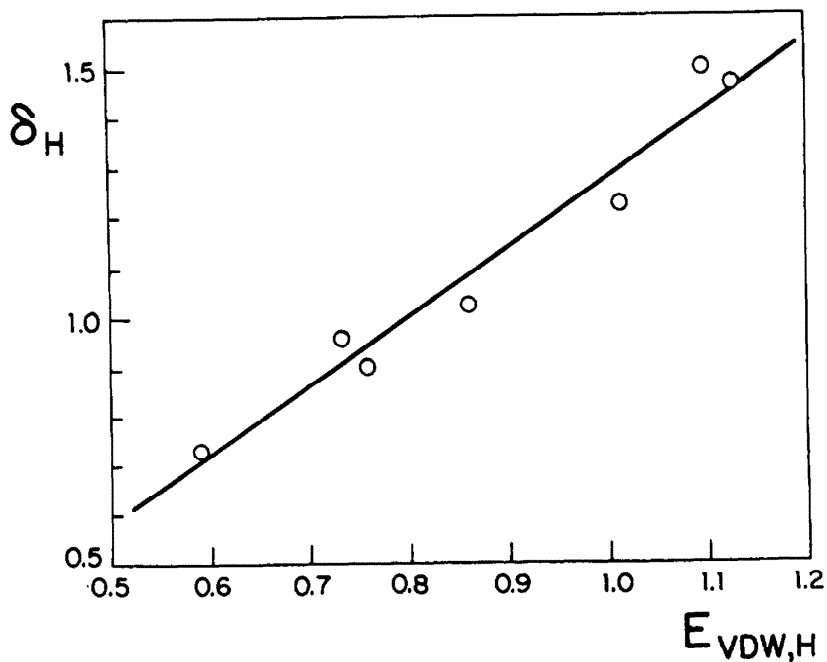


Fig. 3. Observed chemical shift (δ) of the methine protons vs. local van der Waals' energy in cyclohexanes (compounds.....).

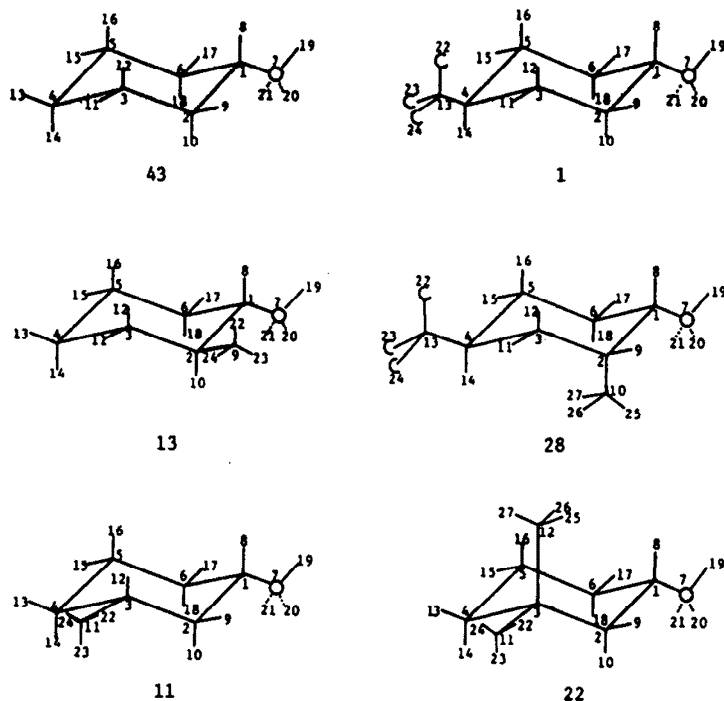


Fig. 4. Atomic numbering for cyclohexanes and cyclohexanols in Table 6.

Table 4.* Chemical Shifts and E_{VDW} of Methine Protons in Cyclohexanes

Compound	Position of H	δ_{obs}	E_{VDW}	δ_{calc}	$\Delta\delta(obs-calc)$
<u>cis,cis</u> -1,3,5-tri-Me-cyclohexane	H _(1a)	1.40	0.7604	1.44	-0.04
<u>cis,trans</u> -1,3,5-tri-Me-cyclohexane	H _(1e)	2.00	1.1012	1.91	0.04
	H _(3a)	1.52	0.8635	1.58	-0.06
CH ₃ (1a)- <u>trans</u> -decalin	H _(1e)	1.72	1.0196	1.80	-0.08
CH ₃ (1e)- <u>trans</u> -decalin	H _(1a)	1.23	0.5900	1.20	0.03
CH ₃ (2a)- <u>trans</u> -decalin	H _(2a)	1.46	0.7360	1.40	0.06
CH ₃ (2a)- <u>trans</u> -decalin	H _(2a)	1.96	1.1304	1.95	0.01

* δ_{obs} come from ref. 12.

Table 5. Results of Regression Analyses

System	Carbinol H	Methylene H	Methine H
correlation coefficient (r)	0.848	0.899	0.977
constant c_{VDW}	2.375	3.634	1.389
constant b	1.537	-0.129	0.383
RMS error (ppm)	0.19	0.20	0.07
99.9% r_{test}	0.490	0.693	0.951

herefore 4-t-butyl has a shielding effect on the carbinol proton. If a methyl group replaces hydrogen 9 on carbon 2, two significant changes appear: First, the repulsive van der Waals'

interaction between atom 9 and the carbinol proton is reduced (from 0.200 with hydrogen 9 to 0.128 with carbon 9). Second, of the three new hydrogens on the methyl group, one of them is located in weak, repulsive van der Waals' interaction region of the carbinol proton (+0.0322), the other two are in the more attractive van der Waals' interaction region (-0.0823). The net result is that the repulsive van der Waals' interaction energy of the carbinol proton is considerably reduced. Therefore, a 2-equatorial methyl group causes an axial carbinol proton to shift upfield. If the substituent is a 2-axial methyl group, although all of the atoms in the methyl group are located in an attractive van der Waals' interaction region of the axial carbinol proton, the methyl group pushes the equatorial hydrogen on carbon 2 much closer to the carbinol proton, and pushes almost all of the other atoms located in the repulsive van der Waals' interaction region closer to the carbinol proton. Therefore, the 2-axial methyl group indirectly raises the repulsive van der Waals' interactions with the axial carbinol proton to a value larger than the attraction produced by itself. The net effect is deshielding. If a methyl group replaces hydrogen 11 on carbon 3 (3-equatorial methyl group), it will lead to both the repulsive and attractive van der Waals' interactions increasing, and the net effect is very small shielding (see Table 6). When we compare *cis*-3-methylcyclohexanol with 3,3-dimethylcyclohexanol, it can be seen that a *syn*-axial methyl group will produce a repulsive interaction which is larger than the attraction to the axial carbinol proton. The net effect is deshielding.

Table 6^ψ. VDW Energy Contribution of the Atoms in Different Molecules to H_e, H_a or carbinol H

No. of atom	H _e in cyclohexane	H _a in cyclohexane	Molecule					
			4 [*]	1 [*]	13 [*]	28 [*]	11 [*]	22 [*]
3	-0.0531	+0.1022	+0.0972	+0.1008	+0.0985	+0.1135	+0.0907	+0.0434
4	-0.0354	-0.0538	-0.0538	-0.0537	-0.0538	-0.0538	-0.0538	-0.0538
5	-0.0531	+0.1022	+0.0969	+0.0981	+0.0973	+0.1137	+0.0999	+0.0884
9	+0.1707	+0.2040	+0.2000	+0.1944	+0.1289	+0.3297	+0.2022	+0.1899
10	+0.2039	-0.0540	-0.0541	-0.0543	-0.0540	-0.0526	-0.0542	-0.0538
11	-0.0273	+0.0092	-0.0271	-0.0280	-0.0271	-0.0285	-0.0243	-0.0220
12	-0.0139	-0.0273	+0.0068	+0.0193	+0.0068	+0.0265	+0.0216	+0.0168
13	-0.0059	-0.0158	-0.0157	-0.0135	-0.0156	-0.0139	-0.0158	-0.0153
14	-0.0158	-0.0198	-0.0196	-0.0208	-0.0196	-0.0209	-0.0197	-0.0194
15	-0.0273	+0.0091	-0.0271	-0.0279	-0.0272	-0.0286	-0.0272	-0.0268
16	-0.0139	-0.0273	+0.0076	+0.0133	+0.0075	+0.0219	+0.0087	-0.0057
17	+0.1797	+0.2040	+0.1972	+0.1986	+0.2024	+0.2300	+0.1998	+0.2047
18	+0.2040	-0.0540	-0.0542	-0.0542	-0.0541	-0.0540	-0.0541	-0.0542
19			+0.1321	+0.1361	+0.1121	+0.1633	+0.2777	+0.2880
20			-0.0146	-0.0145	-0.0151	-0.0128	-0.0146	-0.0136
21			+0.2767	+0.2701	+0.2980	+0.2666	+0.1313	+0.1420
22				-0.0117	+0.0322	-0.0120	-0.0108	-0.0092
23				-0.0045	-0.0542	-0.0046	-0.0059	-0.0052
24				-0.0043	-0.0281	-0.0044	-0.0071	-0.0070
25						-0.0136		+0.2804
26						-0.0277		-0.0499
27						-0.0240		-0.0232
ΣH in Bu				-0.0308		-0.0315		
Σ + E _{VDW}	+0.7493	+0.6307	+1.0145	+1.0307	+0.9837	+1.2652	+1.0319	+1.2536
Σ - E _{VDW}	-0.2457	-0.2520	-0.2662	-0.3182	-0.3488	-0.3829	-0.2875	-0.3591
Σ E _{VDW}	+0.5036	+0.3787	+0.7483	+0.7125	+0.6349	+0.8823	+0.7444	+0.8945

^ψEnergies are in kcal/mol.

*These numbers are compound numbers in Table 2.

From the above, it can be seen that the long distance interaction between substituents and resonant protons occurs by two different mechanisms. One is that the van der Waals' interaction is produced between them directly through the space. The second is that the van der Waals' interaction is relayed by the other atoms in the molecule through geometric deformations (conformational transmission).

Chemical Shifts of Protons in Cyclic Systems.

There are several empirical rules for the chemical shifts of protons in six-membered ring systems:

1. In saturated six-membered ring systems, generally, the axial proton is upfield of the equatorial proton.^[14] According to our model of cyclohexane, E_{VDW} axial (0.39) is much smaller than E_{VDW} equatorial (0.50). From Table 6 it is clearly seen that the equatorial proton is located in the strong repulsive region of four protons on adjacent carbons, but the axial proton is so located for only two of them. It also interacts with carbons 3 and 5 only in the moderately repulsive region, and with the other two syn-axial protons in the weak repulsive region. The total attractive interaction for the axial proton is also larger than that for equatorial proton. Therefore, the axial proton is usually upfield of equatorial proton in a six-member ring system.

2. The equatorial methyl group will produce a shielding effect on both adjacent equatorial protons and adjacent axial protons.^[14] For cyclohexanol our model is consistent with this observation. From Table 2, for axial protons, the $\Delta\delta_{obs}$ between 1 and 26 is 0.44 ppm ($\Delta\delta_{calc} = 0.27$ ppm), the $\Delta\delta_{obs}$ between 13 and 19 is 0.56 ppm ($\Delta\delta_{calc} = 0.30$ ppm); for equatorial protons the $\Delta\delta_{obs}$ between 2 and 27 is 0.36 ppm ($\Delta\delta_{calc} = 0.11$ ppm), the $\Delta\delta_{obs}$ between 14 and 20 is 0.28 ppm ($\Delta\delta_{calc} = 0.20$ ppm).

For cyclohexanes the axial protons are shielded by an equatorial methyl group, such as the $\Delta\delta_{obs}$ between 1 and 3 (in Table 3) is 0.30 ppm ($\Delta\delta_{calc} = 0.35$ ppm). But the equatorial protons are shielded but little by an equatorial methyl group. Thus, the $\Delta\delta_{obs}$ between 2 and 4 is -0.03 ppm ($\Delta\delta_{calc} = 0.26$ ppm); the $\Delta\delta_{obs}$ between 2 and 15 is 0.01 ppm ($\Delta\delta_{calc} = 0.49$ ppm); the $\Delta\delta_{obs}$ between 2 and 19 is 0.13 ppm ($\Delta\delta_{calc} = 0.53$ ppm). These kinds of protons are shown in Fig. 2 as dashed circles. In this case the magnetic anisotropic effect makes an apparent contribution to the chemical shifts. According to Tribble's results,^[8] in cyclohexanes the magnetic anisotropic effect on these kinds of protons is much larger than in other cases.

3. An axial methyl group will shield the adjacent equatorial proton and deshield four of five axial protons.^[14] The axial methylcyclohexane is used as an example. The E_{VDW} for all of the equatorial and axial protons are listed in Table 7. The positive $\Delta\delta$ is shielding, negative is deshielding. The results show that our model predicts this observation well.

Table 7. Shield Effects of Axial Methyl Group on Protons in Cyclohexane

Proton	E_{VDW}	ΔE_{VDW}^*	$\Delta\delta_{obs}$	$\Delta\delta_{cal}$
H _{2e,6e}	0.4204	0.0831	0.40	0.31
H _{3e,5e}	0.5162	-0.0127	-0.08	-0.05
H _{4e}	0.4902	0.0133	0.12**	0.05
H _{2a,6a}	0.4793	-0.1007	-0.20	-0.37
H _{3a,5a}	0.4386	-0.0600	-0.25	-0.22
H _{4a}	0.3874	-0.0088	-	-0.03

* ΔE_{VDW} is the difference of E_{VDW} of the proton between axial methylcyclohexane and cyclohexane. Energy in kcal/mol, $\Delta\delta$ in ppm.

** This value came from cyclohexanol systems.

Here we should point out that, according to the bond anisotropies, there are major discrepancies^[4] in some effects of axial and equatorial methyl groups; but our model is generally consistent with the observation. The results for comparison of these two models are shown in Table 8.

Table 8. Comprison of our Model with Bond Anisotropy

added group	compound pair*	$\Delta\delta_{\text{obs}}^{**}$	$\Delta\delta_{\text{calc, our}}$	$\Delta\delta_{\text{calc Eliel}}^{***}$
axial methyl	33 -- 15	-0.17	-0.35	+(shielding)
"	15 -- 21	-0.17	-0.22	"
"	11 -- 22	-0.20	-0.34	"
equatorial methyl	1 -- 26	0.44	0.27	0.12
"	13 -- 19	0.56	0.29	0.12

*The number of compound pairs is the same as Table 2.

** $\Delta\delta$ is in ppm positive is shielding, negative is deshielding.

***These results were calculated by Eliel et al.^[4] using Musher's method.^[3]

4. Unusual upfield proton chemical shifts in substituted cyclohexanes.

Muller and Tosch^[5] pointed out that the chemical shifts of some ring protons in cis-1,3-dimethylcyclohexane and in cis-1,1,3,5-tetramethylcyclohexane were farther upfield than those of the methyl protons, and that could not be understood using only anisotropic susceptibility theory. Later, Booth^[14] used the empirical parameters of substituents to explain that the chemical shifts of axial protons between two equatorial methyl groups would be farther upfield than would the methyl protons. Segre and Musher^[13a] showed that this was also true for the cis-1,3,5-trimethylcyclohexane and cis, trans-1,3,5-trimethylcyclohexane.

Our calculated δ -values for axial protons between two equatorial methyl groups for all of the above substituted cyclohexanes are consistent with the observations (see Table 9).

Table 9.* δ_{calc} of Unusual Upfield Protons in Some Cyclohexane Systems

R-cyclohexane	δ_{obs}	$\delta_{\text{calc.}}$	$\delta_{\text{CH}_3(\text{eq.})}$	$E_{\text{VDW H}}$
<u>cis</u> -1,3-di-Me	0.37	0.38	0.8	0.1726
<u>cis</u> -1,3,5-tri-Me	0.47	0.38	0.86	0.1715
<u>cis, trans</u> ,-1,3,5-Me ₃	0.47	0.46	0.83	0.1931
<u>cis</u> -1,1,3,5-Me ₄	<0.8	0.43	0.8	0.1860

* δ in ppm, E_{VDW} in kcal/mol.

5. In a trans-1,4-disubstituted cyclohexane, the difference between the chemical shifts of the axial and equatorial protons is much larger than in a cis-1,4-disubstituted cyclohexane.^[5] In order to learn the reason for this, trans-1,4-dimethylcyclohexane and cis-1,4-dimethylcyclohexane were studied. The results of the calculations are presented in Table 10.

Table 10.* Diminution of Difference of δ_a and δ_e in the cis-1,4-isomer

R-cyclohexane	$E_{\text{VDW } 2a}$	$E_{\text{VDW } 3a}$	$E_{\text{VDW } 2e}$	$E_{\text{VDW } 3e}$	$\Delta E_{\text{VDW, e-a}}$	$\Delta\delta_{e-a}$
<u>trans</u> -1,4-dimethyl	0.2750	0.2750	0.4332	0.4332	0.1582	0.58
<u>cis</u> -1,4-dimethyl	0.4726	0.3505	0.4158	0.4483	0.0653-0.0245	0.24-0.1

*Energy in kcal/mol, $\Delta\delta$ in ppm.

From Table 10 it is clear that in the trans-1,4-isomer the difference between the chemical shifts of the axial and equatorial protons is very large (0.58 ppm), but in the cis-1,4-isomer, the difference is small. The chemical shifts of the equatorial protons are located between the chemical shifts of axial protons, and the chemical shifts of all of the axial and equatorial protons are close to each other. The differences between one another are 0.24, 0.12 and 0.1 ppm. Musher had not distinguished which chemical shifts of protons in cis-1,4-isomer were axial or equatorial. The general effect is that the difference of chemical shifts between axial and equatorial protons in the cis-1,4-isomer is very small compared to the trans-1,4-isomer. Our model gives a good explanation of this observation.

Simple Theoretical Considerations

The effect of intramolecular van der Waals' interactions on chemical shifts of protons has been observed for many years. In 1963 Schaefer, Reynolds, and Yonemoto^[15] pointed out that the "anomalous" low-field chemical shifts of protons in some of aliphatic and aromatic halides could not be understood by means of bond anisotropy theory alone, and suggested that intramolecular van der Waals' interactions might be an important cause of these anomalous low-field chemical shifts. In 1968 Cheney^[6] proposed that crowding between H and H' would produce a van der Waals' repulsive force which would induce charge polarization in the C-H bond, and cause a downfield chemical shift of proton H. The general observation of the intramolecular van der Waals' effect on the chemical shifts of protons is that crowding leads to a downfield shift of the protons.^[16] Our recent studies have shown that the intramolecular van der Waals' interaction is general, and is the main factor controlling the steric effect of the chemical shifts of ¹³C, ¹⁵N, and ³¹P in aliphatic systems.^[9]

From perturbation molecular orbital theory, the shielding constant σ contains several contributions:

$$\sigma = \sigma_d + \sigma_p + \sigma_{NM} + \sigma_{VDW} + \sigma_{oth}$$

where $\sigma_d = \frac{e^2}{3mc^2} \sum_{\mu} p_{\mu\mu} \langle \phi_{\mu} | r^{-1} | \phi_{\mu} \rangle$ is the diamagnetic contribution,

and $\sigma_p = \frac{2}{3} \frac{eh}{me} \sum_{\mu} \Delta E^{-1} \langle 2p_N | r^{-3} | 2p_N \rangle \sum_{M} q_{MN}$ is the paramagnetic contribution.

$\sigma_{NM} = \frac{1}{3N_0} \sum_{M \neq N} \Delta \chi_M (1 - 3 \cos^2 \theta) R^{-3}_{NM}$ is the neighboring effect from bond anisotropic magnetic

susceptibility, σ_{VDW} is the van der Waals' contribution, σ_{oth} is the sum of other effects including delocal current, electric field...etc.

For heavy atoms, σ_p is the main factor controlling the chemical shifts of a resonant nucleus. In this case σ_{VDW} was considered to expand or contract the p orbitals of the resonant nucleus, which leads to a decrease or increase of the r^{-3} term, which in turn causes an upfield or downfield effect.^[9]

For protons the general idea is that the main factors are σ_d and σ_{NM} . The quantity is σ_d is mainly associated with the charge ($p_{\mu\mu}$) on the proton. The value of σ_{NM} is dependent on the structure of the compound, and it has an important role in unsaturated compounds. The σ_{VDW} is normally only considered in cases of unusual congestion.^[16]

According to the present work, the main factor controlling the neighboring effect on chemical shifts of protons in saturated hydrocarbons and aliphatic alcohols is σ_{VDW} . The intramolecular van der Waals' interaction can be qualitatively considered as changing the charge on the resonant protons. The environment of a hydrogen in a molecule is different from that of an isolated hydrogen atom. If a hydrogen atom in a hydrocarbon feels an attractive van der Waals' interaction, its effective nuclear charge will be increased, hence some electronic charge will be transferred from carbon to hydrogen, and this leads to an upfield effect on the chemical shift of the proton. Conversely if the repulsive van der Waals' interaction is increased, it will lead to a transfer of electron density from hydrogen to carbon, and produce a downfield effect on the chemical shifts of the proton.

Limitation of theory; sources of error.

As it was discussed in our previous paper^[9], the constant, b , called the class constant or local environment constant, actually includes the α -effect and the effect of the other terms of local steric energy. There is no doubt that the smaller the change in the local environment, the better the linear correlation between δ_H and E_{VDW} that is obtained. From Table 2 and Fig. 1, it is clearly seen that most of the large errors appear in compounds that have ortho-t-butyl (compounds 5 and 6), ortho-isopropyl (compounds 7, 8, 17, 18, 42), or two or more substituents on the carbon ortho to a carbinol proton (compounds 19, 25, 30, 32). This means that in these cases the local environment changes too much to keep b as a constant. If we split all of the more crowded compounds except compounds 6, 8, 18 and 42, into another group, then two linear lines are obtained (dot lines in Fig. 1), and the RMS error will be reduced to 0.1 ppm. If we put compounds 6, 8, 18 and 42 together, although their E_{VDW} are overestimated very much, they seem to be located on another line, and the slopes of these three lines are somewhat different.

Why are the E_{VDW} of cis-2-t-butyl- and cis-2-isopropyl-cyclohexanes overestimated so much? One reason is that the hydrogen atoms in the MM2 force field are somewhat too hard¹⁷, and when they are very close the E_{VDW} increase is too great.

On the other hand, Table 8 shown some substituent effects are overestimated, and some of them are underestimated by our model. If the bond anisotropy effect were to be considered at the same time, the results should become better. It will be worth studying how to combine these two effects together to better understand the steric effects on chemical shifts.

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