Carbon-13 Nuclear Magnetic Resonance Substituent-Induced Shieldings and Conformational Equilibria in Cyclohexanes[1]

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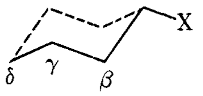
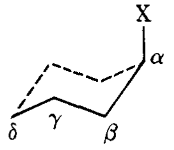
^{13}C NMR shifts induced by the most common hetero substituents are reported for a series of conformationally homogeneous cyclohexanes and alkylated derivatives. The magnitude and in specific cases even the sign of substituent effects on ^{13}C shifts depend strongly on the substitution pattern of the observed alkane. Existing mechanisms and hypotheses for ^{13}C shieldings in hetero-substituted alkanes are examined; only the gross changes in functional carbon (C_α) shifts can be related to MO calculated electron densities, as shown with several norbornane derivatives. The method for measurement of conformational equilibrium constants by low temperature ^{13}C NMR spectroscopy is evaluated. $\Delta G°$ values thus obtained and supplemented by ^1H NMR measurements are discussed for mono- and disubstituted derivatives and compared to literature results and force field calculations.

^{13}C shifts belong to the most important spectroscopic information relating to molecular geometry and charge distribution in carbon compounds.[2] Further development of this promising tool requires the theoretical understanding of shielding mechanisms[3] supported by experimental values as observed with geometrically well-defined model compounds or, at least, a self consistent picture of the experimental shifts, conveniently described as substituent effects $\Delta\nu$ on shielding.[3c] The latter approach should ultimately furnish empirical structure shielding relationships as pioneered for pure hydrocarbons by Grant and co-workers.[4] Before physical significance can be ascribed to postulated relations or before any effects can be applied to unknown molecular structures, it is mandatory to investigate a large number of geometrically related compounds and to analyze the results with more rigorous standards of correlational chemistry.[5]

The shifts observed on α, β, and γ carbons upon introduction of substituents X in the equatorial (e) or axial (a) position of cyclohexane will have the broadest applicability in aliphatic chemistry. **1e** and **1a** contain the most common arrangements of gauche (**1g**) and trans (**1t**) oriented bonds in carbon chains, without substantial deviations from normal sp^3 hybridization. That observation of conformationally inhomogeneous compounds can destroy the inherent information is demonstrated by the results of an earlier study.[6] Here it was reported that for C_α only a very rough correlation exists between substituent X electronegativities (x_p) and shifts, that for C_β and C_γ no relation to X properties exists, and that for C_δ a representation, regarded as satisfactory, as a function of X Taft constants σ^* exists. Ironically, the investigation of conformationally pure cyclohexanes[7] leads to quite satisfactory C_α–x_p correlations (see below); the apparent C_δ–σ^* correlation vanishes, and C_δ, C_β, and eventually C_γ shifts can be represented in terms of electrical field effects[8] depending on X. We have attained conformational homogeneity by either locking cyclohexanes by *tert*-butyl groups and in some cases by methyl groups or by observing cyclohexane conformers at temperatures low enough for slow interconversion on the ^{13}C NMR time scale. The latter approach offers at the same time a promising opportunity to measure conformational equilibria.



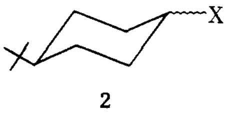
1e (**1t**)



1a (**1g**)

Based on the Pople–Karplus approximation of the paramagnetic screening constant,[3a,c] it is often implied or explicitly claimed[9] that ^{13}C shifts in aliphatic compounds show linear dependence on electron densities as available through semiempirical or ab initio quantum mechanical[3b,d,10] calculations. The ambiguities involved, particularly for heavier elements with parametrization of overlap and coulomb integrals,[11] with the possible inclusion of d orbitals and the mixing in of excited states, can lead to serious deviations;[10] but for the very gross changes of functional carbon shifts ($\Delta\nu \sim 60$ ppm from X = H to X = F) a satisfactory correlation to the charge distribution Q is usually obtained. For stereoisomeric 2-norbornanes very similar slopes for *exo*-2- and *endo*-2- compounds are observed with 265 and 269 ppm/e by INDO[11] (Figure 1); correlations of similar quality ($r = 0.98$; $\psi = 22\%$) are obtained with CNDO/2 calculated[11] charges (334 or 338 ppm/e, respectively). Substituent effects on β or γ carbon atoms, however, which are more reliable for stereochemical assignments (see below), fail to show any meaningful relation to CNDO/2 or INDO calculated charge densities[10] (Figure 2). The inadequacy of the available approximate wave functions to reproduce the stereochemically significant shieldings is not unexpected since even within the ground state limitation the Mulliken population would be required accurate to at least 1% on the 200–300 ppm/e scale. Another approach by calculation of classical electric field effects seems to hold more promise[12a] at the present time.

Preliminary results had shown that the magnitude and even the sign of substituent effects can change upon introduction of additional alkyl groups in the α, β, or γ positions. We therefore have prepared and measured cyclohexanes of types **1**–**7** featuring different substitution patterns on the functional carbon and the observed carbon atoms (Tables I–IV). For



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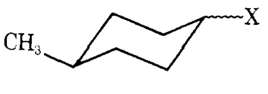

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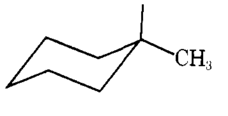

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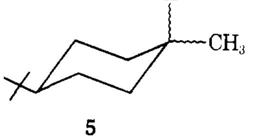

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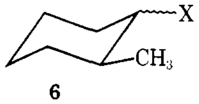

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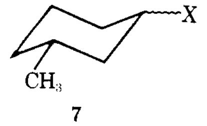

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Table I. Substituent Effects on ^{13}C Shifts[a] in Cyclohexanes (C) and 4-*tert*-Butylcyclohexanes (B)

no.	system	X	pos	registry no.	C_α	C_β	C_γ	C_ϑ	C_ϵ	C_ζ	other C[d]
1	C	F	e		64.54	5.56	−3.37	−2.51			
			a	372-46-3	61.10	3.11	−7.17	−2.02			
2	B	Cl	e	13145-48-7	32.69	10.47	−0.46	−1.89	−0.39	−0.20	
			a	13131-74-3	32.30	7.16	−6.89	−0.92	−0.13	−0.20	
3	B	Br	e	5009-37-0	25.00	11.30	0.70	−2.02	−0.33	−0.22	
			a	5009-36-9	27.50	8.12	−6.28	−1.12	−0.33	−0.22	
4	B	I	e	16133-42-9	2.10	13.81	2.40	−2.42	−0.07	−0.02	
			a	16133-41-8	9.50	9.54	−4.50	−0.80	−0.07	−0.02	
5	B	OH	e	21862-63-5	44.13	8.52	−2.27	−1.50	−0.33	0.06	
			a	937-05-3	38.93	5.95	−6.89	−0.59	0.00	−0.06	
6	B	OCH_3	e	15876-31-0	52.90	5.23	−2.01	−0.72	−0.07	−0.12	55.18
			a	15875-99-7	47.70	3.06	−6.30	−0.07	+0.26	−0.12	55.31
7	C	$OSiMe_3$	e	13871-89-1	43.46	8.99	−2.30	−1.95			
			a		39.13	6.05	−7.18	−1.95			
8	C	OOCH	e		44.94	4.32	−2.96	−2.38			160.34
			a	4351-54-6	41.43	2.17	−6.86	−1.99			160.34
9	B	$OOCCH_3$	e	1900-69-2	46.53	4.75	−2.33	−1.50	−0.33	0.00	21.25 (CH_3), 170.09 (CO)
			a	10411-92-4	42.31	3.15	−6.11	−1.05	−0.07	−0.14	21.38 (CH_3), 170.35 (CO)
10	B	$OOCCF_3$	e	7600-15-9	51.77	4.19	−2.37	−1.62	−0.29	−0.03	114.77 (CF_3), 156.25 (CO)
			a	7556-86-7	48.13	2.83	−6.33	−1.16	−0.29	−0.03	114.77 (CF_3), 156.15 (CO)
11	C	$OOCC_6H_5$	e	2412-73-9	45.78	4.45	−2.90	−2.31			164.83 (CO), 130.58 (C_1')
			a		41.95	2.30	−6.67	−2.31			129.67 (*o*), 128.24 (*m*), 132.72 (*p*)
12	B	OTs	e	7453-05-6	55.51	5.49	−2.24	−2.01	−0.46	−0.10	21.51 (CH_3), 144.30 (C_1'), 127.59 (*o*)
			a	7453-04-5	52.22	3.87	−6.66	−1.36	−0.46	−0.10	129.73 (*m*), 135.00 (*p*)
13	C	SH[c]	e	1569-69-3	11.08	10.69	−0.62	−2.44			
			a		8.93	6.07	−7.58	−1.26			
14	B	NH_2	e	2163-34-0	23.91	9.95	−1.62	−1.31	−0.40	0.00	
			a	2163-33-9	18.07	6.50	−7.22	−0.33	−0.20	0.00	
15	B	$HNCH_3$	e	2523-81-1	32.11	6.25	−1.75	−0.72	−0.26	0.00	34.19
			a	2523-80-0	26.78	3.19	−6.56	−0.14	−0.26	0.00	34.19
16	B	$N(CH_3)_2$	e	2523-69-5	37.08	1.72	−1.13	−0.64	−0.33	0.00	41.73
			a	2523-68-4	33.70	2.63	−6.20	+0.33	−0.33	0.00	43.74
17	C	N_3	e	19573-22-9	32.46	4.45	−2.51	−2.51			
			a		29.80	2.04	−6.86	−1.80			
18	C	NC	e	931-53-3	24.86	6.67	−2.64	−1.82			153.78
			a		23.29	3.52	−6.87	−1.82			155.34
19	C	NCS	e		28.31	6.90	−2.48	−2.17			127.16
			a	1122-82-3	25.83	4.29	−6.44	−2.17			128.59
20	B	NO_2	e	7214-34-8	58.02	4.02	−2.42	−1.98	−0.33	0.01	
			a	7214-33-7	53.87	1.72	−5.64	−1.13	−0.33	0.01	
21	B	CH_3	e	4001-94-9	5.66	8.59	−0.18	−0.65	−0.27	0.00	22.75
			a	3325-80-2	0.13	5.54	−6.49	0.13	−0.27	0.00	17.49
22	C	$-C\equiv CH$	e		1.65	5.10	−1.79	−2.05			88.65 (C_1'), 68.25 (C_2')
			a	931-48-6	1.01	3.02	−5.82	−1.34			87.29 (C_1'), 70.00 (C_2')
23	C	-CN[c]	e	766-05-2	0.74	2.17	−2.57	−2.57			122.65
			a		−0.56	0.35	−5.11	−1.99			121.99
24	B	H[d]		3178-22-1	26.91	27.42	27.88	48.69	32.63	27.62	

[a] In ppm (±0.05 ppm) relative to X = H; measured with **2** (B; 20% in $CDCl_3$ at 298 K), or, if not available, with **1** (C; 20% in $CFCl_3$ at 180 ± 1 K), unless indicated otherwise. For other data, see supplementary material (Table Ia) and ref 7d. [b] At 170 K, 20% in CF_2Cl_2. [c] At 193 K in $CFCl_3$. [d] Shifts relative to Me_4Si (C_6H_{12}, 27.66 ppm).

acyclic compounds[8] satisfactory correlations to cyclohexanes were achieved only after corresponding substitution patterns in cyclohexanes had become available.

The introduction of substituents in 1–7 can lead to deviation from normal cyclohexane geometry, which, although small, can influence the observed ^{13}C shifts. Recent force field calculations[12b] have shown that, contrary to other suggestions,[13] the conformational changes generated by hetero substituents cannot be consistently correlated with the observed ^{13}C shielding effects. Molecular mechanical calculations[14] as well as ^1H NMR spectra[15] suggest substantial ring puckering near a *tert*-butyl group attached to cyclohexane, although in several crystal structure determinations only small deviations from normal cyclohexane geometry, apart from unusually small C_3–C_4–C_5 bond angles,[16] have been found. Whereas an equatorial methyl group leaves the ring essentially undistorted,[17,18] axial alkyl substituents bend outward and give rise to ring flattening as evident from spectroscopical[15,18] and calculational[12b,14,17] investigations. Correlations between ^{13}C substituent effects in cyclohexanes 1 and the corresponding 4-*tert*-butylcyclohexanes 2 are good ($r \geqq 0.90$; $\psi \leqq 20\%$) for C_α and C_β, but they are less reliable for C_γ and hardly visible for C_δ, which indicates geometry distortions progressing in that order.

α **Effects.** The inductive nature of the functional carbon C_α–X shielding mechanism is supported by the long standing relation to X electronegativity.[3] With cyclohexanes, correlations of similar quality ($r > 0.97$; $\psi < 27\%$), again with slopes indistinguishable within the error limit for the stereoisomers, are observed[7d] (Figures 3 and 4). Divalent substituents -X-Y fit in the correlation to X electronegativity if the apparent β' effect of Y on C_α, transmitted over the heteroatom X, is subtracted.[19] Experimentally we find for the β' effect by comparison to -XH: OCH_3, 9.5 and 9.6 ppm; SCH_3, 6.8 and 8.4 ppm; $NHCH_3$, 8.2 and 8.7 ppm; $N(CH_3)_2$, 6.6 and 7.8 ppm, respectively, for equatorial and axial -XY positions.

Introduction of a *tert*-butyl group in the 4 position of cyclohexanes leads to a $\Delta\nu$ enhancement on C_α of up to 1.8 ppm.

Table II. Substituent Effects on ^{13}C Shifts[a] in 1-Methyl-4-*tert*-Butylcyclohexanes

no.	X	pos	registry no.	C_α	C_β	C_γ	C_δ	C_β' (CH_3)
1	F	e	65199-18-0	68.31	5.40	3.70	−1.57	5.84
		a	65199-17-9	60.28	1.40	−5.02	−0.79	5.10
2	Cl	e	25276-10-2	43.29	10.47	3.83	−1.57	10.65
		a	25276-09-9	39.00	5.85	−4.29	−0.79	11.44
3	Br	e	25276-12-4	40.44	10.53	4.15	−1.64	11.50
		a	25276-11-3	38.41	7.21	−3.59	−0.86	13.06
4	I	e	66922-04-1	24.72	14.94	4.09	−1.70	13.97
		a	66922-05-2	26.71	10.05	−1.83	−0.92	16.51
5	OH	e	16980-56-6	43.82	8.13	3.57	−1.05	7.79
		a	16980-55-5	36.26	3.31	−5.02	−0.27	8.71
6	[H[b]	a-CH_3		27.04	32.96	21.39	48.82	17.49]
	[H[b]	e-CH_3		32.57	36.01	27.70	48.04	22.75]

[a] In ppm (±0.05 ppm) relative to the parent *trans*-1-methyl- (axial CH_3 for X position equatorial) and *cis*-1-methyl-4-(*tert*-butyl)-cyclohexanes (equatorial CH_3 for X position axial); measured at 298 ± 1 K, 20% in $CDCl_3$. [b] Relative to Me_4Si.

Table III. Substituent Effects on ^{13}C Shifts in 2-Methylcyclohexanes

no.	X	registry no.	α (C_1)	β (C_2)	β' (C_6)	γ (C_3)	γ' (C_5)	γ'' (CH_3)	δ (C_4)
1	e-CH_3, e-Cl[a]	28046-83-5	31.31	8.05	10.25	−1.28	−0.33	−2.41	−1.89
	e-CH_3, a-Cl[a]	28046-82-4	31.44	7.07	6.35	−7.65	−7.74	−5.75	−2.39
2	e-CH_3, e-Br[a]	28046-85-7	25.63	8.28	11.39	−0.96	0.68	−0.72	−1.81
	e-CH_3, a-Br[a]	28046-84-6	27.38	6.98	6.25	−6.87	−6.02	−4.16	−2.20
3	e-CH_3, e-OH[a]	7443-52-9	39.99	6.89	8.20	−2.26	−1.60	−3.93	−1.55
	e-CH_3, a-OH[b]	7443-70-1	33.43	3.47	6.25	−8.04	−7.51	−3.25	−1.03
	a-CH_3, e-OH[c]		38.68	6.26	10.87	−2.00	−2.45	−6.57	−1.67
4	e-CH_3, a-$OOCCH_3$[b]	15288-14-9	36.29	1.71	2.81	−7.46	−6.99	−3.97	−1.74
	a-CH_3, e-$OOCCH_3$[c]		41.35	3.34	4.04	−2.39	−2.83	−5.99	−1.15
5	e-CH_3, e-NH_2[b]	931-10-2	20.62	7.69	9.11	−1.80	−1.01	−3.51	−1.08
	e-CH_3, a-NH_2[b]	2164-19-4	14.19	2.75	6.51	−8.63	−7.51	−3.25	−1.09
	a-CH_3, e-NH_2[c]		19.64	6.71	11.13	−3.04		−6.77	−1.67
6	e-CH_3, e-CH_3[d]	6876-23-9	3.85	6.78	9.12	0.35	0.39	−1.95	−0.08
	e-CH_3, a-CH_3[e]	2207-01-4	−2.58	2.36	6.70	−7.39	−6.60	−1.69 (−5.66)	−0.05

[a] In ppm (±0.05 ppm) relative to methylcyclohexane (Table Ib in supplementary material, no. 9 equatorial); measured at 298 ± 1 K, 20% in $CDCl_3$. [b] As in *a* but in $CFCl_3$. [c] As in *b* but relative to no. 9 axial, Table Ib. [d] See footnote *d* to Table IB. [e] See footnote *e* to Table Ib.

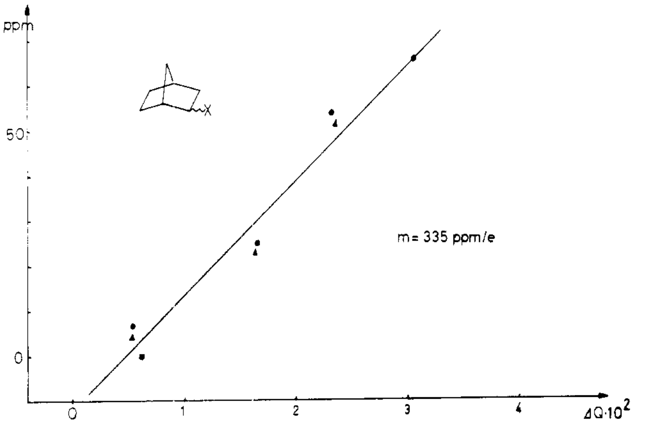


Figure 1. Plot of functional carbon C_2 shifts of 2-norbornane derivatives vs. CNDO/2 calculated electron densities: ● = H, *exo*-CH_3, NH_2, OCH_3, and F; ▲ = H, *endo*-CH_3, NH_2, and OCH_3.

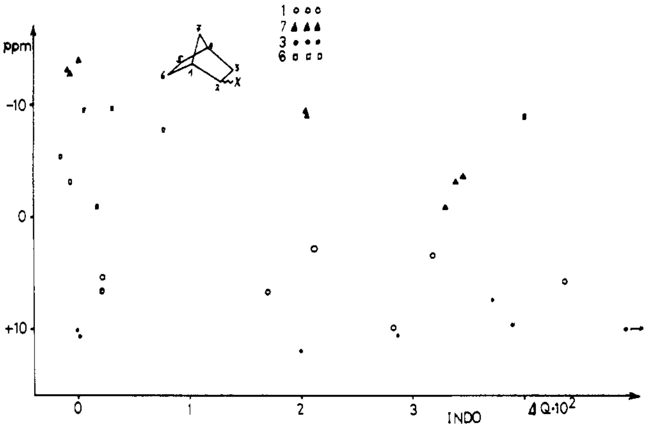


Figure 2. Comparison of C_β and C_γ shifts with INDO calculated electron densities in 2-norbornane compounds.

Since compounds 1 were measured in $CFCl_3$ and 2 in $CDCl_3$ solution at different temperatures, it was secured by control experiments with 2 (X = H, Br, OCH_3) that not more than 0.6 ± 0.2 ppm of $\Delta\nu$ is due to solvent or temperature effects. Methyl substitution at C_3 and C_2 is found to cause variation of the substituent effect of X on C_α by only 5% on the average, but additional alkyl groups at C_1 (α) *enhance* $\Delta\nu$ by up to 23 ppm (5; X = I). These findings are at variance with the often assumed general attenuation effect in tertiary compounds or those containing less hydrogen on α or β carbon atoms, as suggested in an early investigation[20] of alcohols and alkanes. Substituent effect enlargements in tertiary as compared to secondary functional compounds of similar magnitude are found in adamantyl[21] and bicyclo[3.3.1]nonyl[22] derivatives; the deviations of $\Delta\nu$ generally increase with increasing X polarizability.

The possible contribution of neighbor group X anisotropies to C_α shifts is limited to a few parts per million,[3a,c,9] as evident from the magnitude of comparable ^1H shifts. Although the concept of isolable bond anisotropy values is questionable[23] and the application of point dipole derived equations on the

Table IV. Substituent Effects on ^{13}C Shifts[a] in 3-Methylcyclohexanes

no.	X	pos	registry no.	α (C_1)	β (C_2)	β' (C_6)	γ (C_3)	γ' (C_5)	δ (C_4)	δ' (CH_3)
1	Cl	e	28046-86-8	31.96	9.90	10.17	−0.01	−1.42	−2.52	−0.52
		a	28046-87-9	32.25	6.32	7.28	−6.80	−7.10	−2.06	−1.58
2	Br	e	28046-88-0	24.16	10.74	11.20	0.28	−0.38	−1.67	−0.78
		a	28046-89-1	26.79	6.91	7.24	−6.09	−6.36	−1.41	−1.11
3	I	e	66922-06-3	0.99	12.89	13.16	2.49	1.83	−2.71	−2.42
		a	66922-07-4	7.88	8.47	9.45	−4.59	−4.80	−2.00	−1.37
4	OH	e	5454-79-5	43.04	8.34	7.31	−1.67	−3.11	−0.89	−0.26
		a	7443-55-2	39.01	5.35	6.14	−6.74	−7.33	−1.93	−0.72
5	CH_3	e[b]	638-04-0	5.92	9.05	8.99	0.08	−0.48	−0.25	
		a[c]	2207-03-6	−0.98	4.75	4.49	−5.22	−6.58	−0.25	−0.55
6	e-CH_3, e-NH_2[d]		1193-16-4	23.15	9.37	9.46	−1.34	−2.33	−1.74	0.19
	e-CH_3, a-NH_2[d]		1193-17-5	18.60	5.87	5.88	−7.40	−7.40	−0.76	−0.58
	a-CH_3, e-NH_2[e]			23.93	8.92	9.91	0.55	−2.71	−2.20	

[a] In ppm (±0.05 ppm) relative to methylcyclohexane (Table Ib, no. 9 equatorial); measured at 298 ± 1 K, 20% in $CDCl_3$. [b] See footnote *d* to Table Ib. [c] D. Dodrell, C. Charrier, B. L. Hawkins, W. O. Crain, Jr., L. Harris, and J. D. Roberts, *Proc. Natl. Acad. Sci. U.S.A.*, **67**, 1588 (1970). [d] In ppm (±0.05 ppm) relative to methylcyclohexane (Table Ib, no. 9 equatorial); measured at 193 ± 1 K, 20% in $CFCl_3$. [e] As in *d* but relative to no. 9 axial (Table Ib).

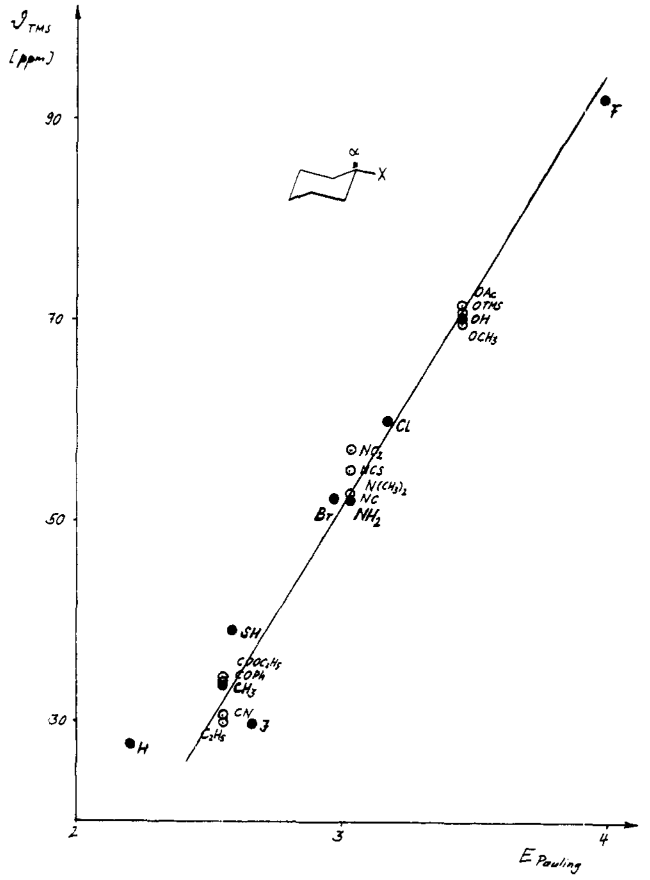


Figure 3. Plot of functional carbon shifts in equatorial-substituted cyclohexanes vs. Pauling electronegativity parameters. Open circles are corrected shifts for second Y at X (see text).

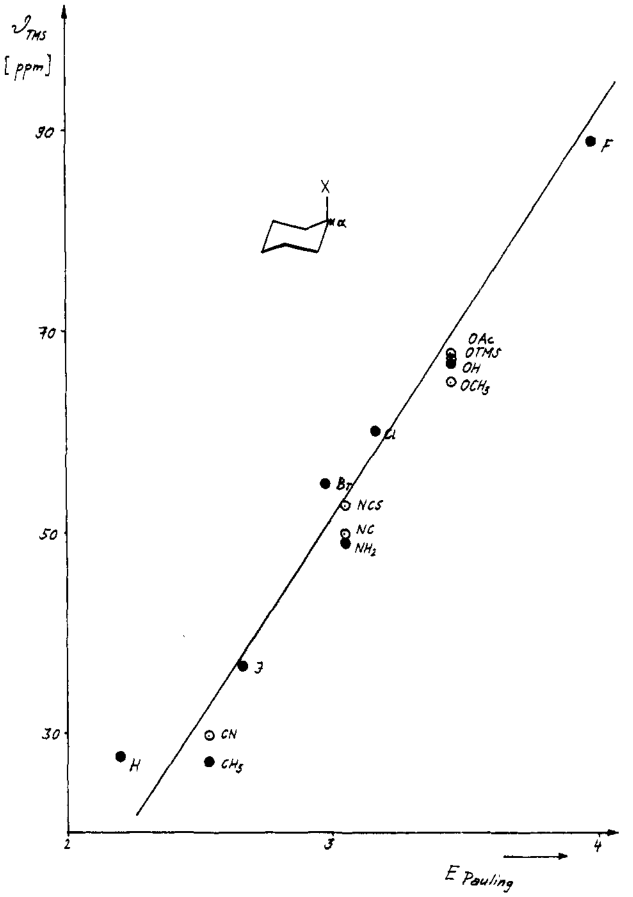


Figure 4. Plot of functional carbon shifts in axial-substituted cyclohexanes as in Figure 3.

screening of nuclei at short distances (as C_α) is misleading,[24] we have estimated some possible anisotropy contributions to C_α shieldings (δ_N) using literature susceptibility values $\Delta\chi$ and standard bond lengths and angles. Following the treatment of ^{1}H shieldings by ApSimon et al.,[25] we obtain for the C=CH group $\delta_N = +0.7$ ppm (deshielding), for C=O +1.0 ppm, for CH_3 +1.7 ppm, and for $-C{\equiv}N$ +2.3 ppm ($\Delta\chi = -28$ cm^3/molecule[26]).

β Effects. The shifts induced on β carbon atoms are far from being independent of the nature of the substituent X, as had been suggested in earlier investigations.[20,27] Deshielding ranging from 3 to 14 ppm is found in cyclohexanes 1 or 2; it can be represented quantitatively as the result of a C_β electron cloud distortion by the fluctuating C_α–X dipole (square electric field or van der Waals effect).[12a,28] A striking feature, not rationalized by square electric field effects, is the constantly smaller β effect (by 3–4 ppm) of axial as compared to equatorial C_α–X groups. This stereochemically useful difference, which was already observed in hydrocarbons,[4] is retained in all cyclohexanes, including the tertiary compounds **4** and **5**, as well as in other systems with gauche/trans arrangements of type **1a** and **1e**.[29] The smaller β carbon deshielding in gauche fragments cannot originate in different charges at C_α since the observed difference in $\Delta\nu$ for C_β does not correlate with C_α shift differences between axial and equatorial X pairs, and secondly the β' effect on CH_3 in **4** and

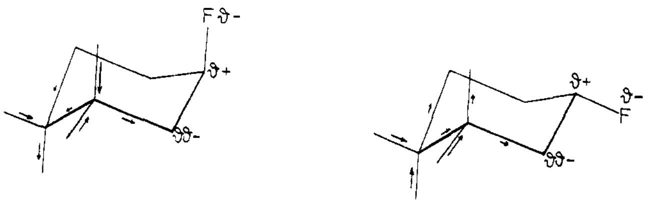


Figure 5. Electron flow generated by the linear electric field effect of point charges[1] (~0.3 electron units at C_α and X; 0.01 electron units at C_β).

5 is very similar to $\Delta\nu$ on C_2 and independent of X orientation. Linear electric field effects could play a minor role[1] since in **1a** one C–H bond of **1e**, which is gauche to C_α–X, is replaced by a more polarizable C–C bond. The estimated accumulation of electron density at C_β, however, is too small to account for the observed difference of 3–4 ppm. A steric origin of the β-shift difference is supported by the results of molecular mechanical calculations,[12b] which indicates rather consistent $C_\alpha C_\beta C_\gamma$ and $XC_\alpha C_\beta$ bond angle widening in axial-substituted cyclohexanes. Additional alkyl groups in the 3 or 4 positions to C_α (**2, 3, 5,** and **7**) or in the 3 position to the observed C_β (C_6 in **6**) exert negligible influence on β substituent effects ($\leq$0.5 ppm). Methyl groups in the 1 or 2 position (**4, 5,** and **6**) lead to similar β $\Delta\delta$ values attenuated by 1–3 ppm.

Anti γ Effects. Electronegative substituents of the second row, such as N, O, or F, are known to produce shielding at a γ carbon in antiperiplanar position.[20,30] The shielding is not substantially altered by additional equatorial alkyl groups (cf. **2, 3, 6,** and **7**), but replacement of the axial C_α–H bond by a C_α–C bond (**4** and **5**) leads to dramatic changes in sign and magnitude of $\Delta\nu$. This sign reversal is *not* limited to bridgehead compounds[22,30,31] but is in fact found in all tertiary derivatives as well as in carbocyclic systems,[22,32] where the axial hydrogen at C_γ is substituted by a C_γ–C bond. The anti γ deshielding by 2.5–4 ppm in these compounds can partially be assigned to linear electric field effects.[1]

The reversal of anti γ shielding effects in systems not containing the specific arrangement of syn axial C–H bonds at C_α and C_γ does not lend support to the suggestion[30] of a hyperconjugative charge transfer from X to C_γ. The alternating shifts at C_α, C_β, and C_γ have been related to the Pople–Gordon[33] charge alternation effect,[7d,34] but several observations, such as increasing β effects from X = F to X = I for example or the shift reversal cited above, are not explicable on this basis. Furthermore, MO calculated charge densities fail to reflect β and γ shifts (Figure 2). It can be shown,[12a] however, that very small electron density accumulations (<2%) at C_β will give rise to shielding electron flows in bonds at C_γ while the corresponding linear field effect at C_δ, generated by the C_α–X dipole, remains essentially unaffected (Figure 5).[35]

Syn γ Effects. Different mechanisms must be responsible for the pronounced shielding of γ carbons in gauche conformations **1a**. Sterically induced charge polarizations along C_γ–H bonds have been invoked for these effects in hydrocarbons.[12b,36] Clearly, the shielding exerted by substituents of small van der Waals radii like fluorine is of a different nature. Linear electric field effects, polarizing mainly the axial C_γ–H bond, correctly predict the sign, although not accurately the magnitude, of the observed shielding.[8,12a] Another factor is likely to result from $n_X{}^*-\sigma_H$ overlap since the lone pair orbitals of heteroatom X are in close contact with the σ_{CH} orbitals of the axial C_γ–H bonds. The magnitude and sign of axial substituent induced shieldings on ring C_γ in cyclohexanes are remarkably independent of the presence of other alkyl groups (**2**–**7**). Notable exceptions are found in cyclohexane[37] and bicyclo[2.2.1]heptane[12,32] compounds, where *de*shielding substituent effects are observed due to the occurrence of axial C_γ–C instead of C_γ–H bonds. Sterically induced charge polarization also is predicted to lead to *de*shielding for certain conformational arrangements,[12b] particularly with sensor groups such as CH_3, which easily change torsional angles. Syn γ effects on methyl carbon shifts, as in **6**, are partially diminished, possibly as a result of widened torsional angles and subsequent smaller 1,4 interaction between γ-CH_3 and X.

Effects on C_δ and More Remote Carbon Atoms. Electronegative substituents invariably shield carbon δ by 1–2 ppm, axial groups in all cases to a significantly lesser degree. Additional alkyl substituents in various ring positions leave the X substituent effects constant to within ±0.3 ppm, unless special solvent susceptibilities are to be expected (as with cyclohexyl iodides) or unless bulkier substituents lead to distortions of the cyclohexane skeleton [see **6** (X = e-CH_3) and **2** (X = a-CH_3)]. δ effects in cyclohexanes bearing X and methyl groups alternatively in equatorial or axial positions (**3, 4, 6,** and **7** with axial X) are obscured if the conformer with the axial methyl cannot be measured separately in low temperature spectra. Since δ carbons are remote from direct interactions with the substituents, their shielding can be represented by linear electric field effects[12a] (Figure 5). Again, CNDO or INDO calculated charge densities fail to reproduce the C_δ shifts, while a frontier orbital treatment at least qualitatively[38] predicts an accumulation of electron density at C_δ by electronegative substituents at C_α.

As to be expected on the basis of linear electric field effects, C_ϵ and C_ζ in **2** are shielded by electronegative C_α substituents by less than 0.5 ppm. The differences for varying X groups are too small to warrant quantitative consideration. They shed light on long range substituent effects in steroids, where in specific cases long range effects above 1 ppm are observable, which must be due partially to conformational (steric) transmission.[39]

Conformational Equilibria. Methods. Valuable information on cyclohexane conformations has been obtained from ^{13}C NMR spectra, particularly of methyl and hydroxy derivatives at room temperature.[40] The advance of new techniques in dynamic NMR spectroscopy opens access to more quantitative measurements of equilibrium constants K. Possible pitfalls in the application of indirect methods, relying mostly on model compounds, have been aptly discussed elsewhere.[41] Time-averaged ^{13}C shifts can be used for the population analysis of rapidly equilibrating species, e.g., *n*-butane, if the temperature dependence of the shieldings is known,[42] but for the more slowly interconverting chair cyclohexane conformers, direct integration of separately visible NMR signals is clearly preferable.[41] The advantage of low temperature ^{13}C over ^1H NMR spectroscopy has been exploited already in several investigations[43–45] and can be seen in (i) the availability of several exchanging signal pairs, yielding 3–4 values for K and consequently numbers for the errors $\Delta\Delta G°$ as given in Tables V and VI, (ii) the wide spread of shift differences between exchanging signals, enhancing the observable temperature range, and (iii) the simplicity of the proton noise-decoupled spectra without additional isotopic substitution.

As with ^1H NMR spectroscopic signal integration,[41] the use of ^{13}C signal intensities requires some general precautions. Differences in T_1 relaxation times for stereoisomeric carbon atoms can lead to erroneous intensities in PFT accumulated spectra if relaxation is slower than pulse repetition. For this and other reasons (see Experimental Section), we have applied smaller pulse angles, which generate only minor distortions of the Boltzmann equilibrium.

That saturation effects do not affect the observed intensity ratios in cyclohexanes at 180 K (lifetime $\tau \sim 0.1$ s) was secured by an experiment applying pulse angles of 18, 35, and 90° (pulse delay 10 s) to a solution of cyclohexyl bromide in $CFCl_3$. Intensity ratios from all 4 carbon signals of 19.9, 20.5, and 19.8,

Table V. Free Energy Differences ($\Delta G°$) of Monosubstituted Cyclohexane Conformers[a]

			^{13}C NMR-PFT		^{1}H NMR-PFT		^{13}C NMR	^{1}H NMR
X	registry no.	temp	$\Delta G°$	$\pm\Delta\Delta G°$	$\Delta G°$	$\Delta\Delta G°$	(ref 44a)[b]	(ref 41)[b]
F		180	0.360	0.025			0.38	0.270
Cl	542-18-7	180	0.507	0.04	0.539	0.055	0.53	0.52
Br	108-85-0	180	0.485	0.025	0.478	0.025	0.61	0.48
I	626-62-0	180	0.490	0.02			0.59	0.47
OH	108-93-0	193	1.01	0.03			1.01[40c]	0.97
OH		190	1.11[d]	0.04[d]				
OCH_3	931-56-6	180	0.750	0.035				0.56 (OCD_3)
OOCH		180	0.617	0.02	0.602	0.040		0.59
$OOCCH_3$	622-45-7	180	0.785	0.03	0.774	0.035		0.71
$OOCCF_3$	1549-45-7	180	0.575	0.02				0.54
$OOCC_6H_5$		180	0.500	0.022				
$OSiMe_3$		170	0.735	0.02				
OTs	953-91-3	190	0.475	0.035	0.409	0.033		0.52
OTs		190	0.445[d]	0.04[d]				
NH_2	108-91-8	193	1.23	0.03			1.45[c]	1.10
-NC		180	0.190	0.01				0.21
NCS		180	0.206	0.02				0.28
N_3		180	0.622	0.022	0.587	0.042		0.75
NO_2	1122-60-7	193	1.13	0.03			1.27[44b]	1.05
SH		193	1.22	0.04				1.20
$-C{\equiv}CH$		182	0.515	0.012				0.41
CN		178	0.214	0.02				0.24

[a] $G°$ is in kcal/mol; temperature is in K; 20% in $CFCl_3$ with 5% Me_4Si, if not otherwise noted. [b] Literature $\Delta G°$ values as indicated, if not noted otherwise. Conditions for ref 44a: 20–30% in CS_2 (RF with acetone and methanol) at 183–195 K. For ref 41: 20% in CS_2 at 190–200 K. [c] Reference 45b; $\Delta G°$ calculated from *cis*-4-methylcyclohexylamine. [d] CS_2.

Table VI. Free Energy Difference ($\Delta G°$) of Disubstituted Cyclohexane Conformers[a]

Y	registry no.	$\Delta G°$	$\pm\Delta\Delta G°$	$\Delta G°$(calcd)[b]
a-1-Cl	931-78-2	1.07	0.03	1.14
a-1-Br	931-77-1	1.19	0.03	1.17
a-1-OH	590-67-0	0.31	0.04	0.73
a-1-OH		0.335[e]	0.05[e]	
a-1-$OOCCH_3$	16737-30-7	0.775	0.04	0.85
a-2-OH		0.67	0.05	0.73
a-2-$OOCCH_3$		0.76	0.03	0.85
a-2-NH_2		0.57	0.03	0.51
a-3-OH[d]		>1.2		0.73
a-3-$OOCCH_3$[c]	66922-08-5	>1.2		0.85
a-3-NH_2		0.56	0.03	0.51
a-4-OH	7731-28-4	0.83	0.04	0.73
a-4-$OOCCH_3$	13332-20-2	0.93	0.02	0.85
a-4-NH_2	2523-56-0	0.62	0.03	0.51
a-4-*i*-$CHMe_2$[d]	6069-98-3	0.31	0.04	0.39

[a] See footnote *a* in Table V; 192 K unless noted otherwise; X = e-CH_3. [b] Calculated $\Delta G°$ assuming additivity (see text). [c] Estimated from line width near coalescence (see Experimental Section). [d] Isomenthane, at 183 K. [e] CS_2.

respectively, were observed, corresponding to $\Delta G° = 490 \pm 15$ cal/mol.

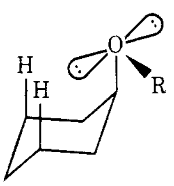
Under proton noise decoupling conditions, differential nuclear Overhauser effects will give rise to deviations of signal areas mainly if, in the case of nonquaternary carbon atoms, the distance between carbon and directly bonded hydrogen does not remain constant.[46] That these differences usually are negligible, if one compares exchanging stereoisomeric carbon atoms, is shown by the consistency of signal area ratios in topomers[7b] and in epimeric mixtures.[47] Here we find the accuracy of quantitative ^{13}C spectroscopy surpassing that of ^{1}H NMR methods. Small but consistent signal area deviations are found only for carbon atoms C_α, which alternatively bear equatorial or axial substituents.[7b,44a,47] Our observation of larger C_α peaks, in most cases by 5%, in **1e** and related compounds supports the interesting suggestion of elongated equatorial as compared to axial C–H bonds in cyclohexanes.[48]

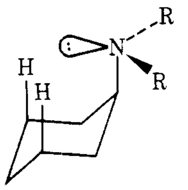
Taking additional precautions for signal integration (see Experimental Section), one can obtain $\Delta G°$ values reproducible and accurate to $\Delta\Delta G°$ = 2–35 cal/mol (Tables V and VI), which we believe to be influenced by systematic errors to a lesser degree than those obtained by previously available methods. Substantial deviations from $\Delta G°$ values obtained by other workers using low temperature ^{1}H or ^{13}C NMR signal integration (see Table V) are noted for compounds where the equilibrium is sensitive either to solvent or substrate concentration changes (as with cyclohexyl iodide) or to concentration dependent hydrogen bonding (as with hydroxy[49] and amino compounds).

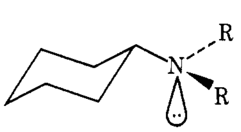
It has been noted that differential saturation can lead to weaker signals for the equatorial isomer in ^{1}H NMR-CW spectra.[41] That some resulting $\Delta G°$ values are indeed too small is supported by our and other[44] ^{13}C NMR values, which are consistently larger. In addition, we have reexamined some equilibria by ^{1}H NMR-PFT spectroscopy in the absence of saturation effects and find better agreement with $\Delta G°$ values determined by ^{13}C NMR spectroscopy (Table V).

Monosubstituted Cyclohexanes. Energies $\Delta G°$ of conformational equilibria should in principle be accessible by quantum mechanical calculations, but here they appear as very small differences between much larger ($\times 10^3$–10^5) total energies. More reliable information and insight into the different contributions to $\Delta G°$ can be expected from semiempirical molecular mechanical calculations, for which cyclohexane equilibria can provide important parametrization numbers. The free energy differences determined for halocyclohexanes by the improved NMR method (Table V and ref 44a) are in substantially better agreement with results from Allinger's extended force field[50] than are earlier values. An inspection of force field[12b,48] results for cyclohexanes suggests that the higher energy for axial halogen and methyl groups resides largely in bond angle distortions and in 1,3 diaxial repulsions, but only for X = a-CH_3 to a substantial degree in the gauche hydrogen interaction[48] of the equatorial hydrogen at C_1. This is the result of the particular outward bending of CH_3, which brings the corresponding equatorial hydrogen in strongly repulsive contact with the vicinal axial hydrogen atoms at C_2.

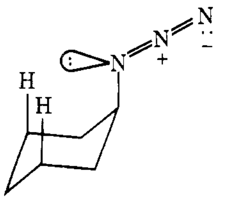
Conformational equilibria in cyclohexanes bearing substituents with lone electron pairs will largely depend on the either attractive[51–53] or repulsive interactions with the axial hydrogen atoms at C_γ. Earlier theoretical calculations suggested substantially smaller repulsions for nitrogen lone pairs as compared to hydrogen at intermediate distances (~3 Å).[53] For tropane compounds with 1,3 distances in the range of 2–3 Å, it could be shown recently by low temperature ^{13}C spectroscopy that the repulsive interactions of an *N*-methyl group are of comparable size to those in cyclohexanes, whereas very similar values are obtained for hydrogen and the lone electron pair at nitrogen.[54] Repulsive interaction between syn diaxial hydrogens at C_γ and lone electron pairs directed at them provides also rationalization of the decreasing destabilization of axial cyclohexyl oxygen derivatives with stronger electron-withdrawing substituents[41] (Table V; X = OCH_3, OMe_4Si, $OOCCH_3$, $OOCCF_3$, $OOCC_6H_5$, OTs). The lower electron density in the oxygen lone pairs is expected to lower the 1,3 repulsion if the rotamer with the substituent R at oxygen pointing away from the ring is dominant. That the rotamer distribution around the C_α–X bond is very similar for equatorial and axial oriented XY groups is supported by the indistinguishable shift of Y in compounds with Y = CH_3 or COR′ (X = O, N).







Substituents with multiple bonds in time-averaged $C_{\infty v}$ symmetry usually exert small repulsive interactions.[41] Their effective van der Waals radii are essentially determined by the electron densities in the outer orbitals.[55] The relatively large $\Delta G°$ value for X = –C≡CH is in excellent agreement with force field calculations[56] and reflects the high density at the carbon directly attached to the ring, which is substantially lowered in the nitrile derivative.[55] While the low $\Delta G°$ values for X = –NC and X = –NCS are understandable on the basis of absent lone electron pairs at N in the most important mesomeric form,[41,57,58] the corresponding azide must dominate in the form containing the lone pair at the N atom bonded at C_α.[57] In agreement with the observation on repulsive interactions between lone pairs at NR_2 or OR and the syn diaxial hydrogen atoms, this leads to the rather high destabilization for a-X = N_3 with $\Delta G°$ = 0.6 kcal/mol.[59]



Disubstituted Cyclohexanes. With the exception of dihalocyclohexanes, the conformational equilibria of polysubstituted rings have rarely been measured by direct NMR methods.[41] They can provide $\Delta G°$ values for groups which shift the equilibrium too much to the **1e** side in monosubstituted cyclohexanes to be measurable, provided one can neglect interactions between the substituents. Distortions transmitted by ring deformations will in addition be recognizable by deviations from additivity of $\Delta G°$ values. These distortions will be minimized in cis 1,4-disubstituted cyclohexanes, such as in isomenthane (**3**; X = $CH(CH_3)_2$). Assuming additivity, one obtains $\Delta G°$ = 2.1 kcal/mol for the isopropyl group; the difference from the methyl group value (1.74 kcal/mol[45a]) is believed to originate in the entropy disadvantage for the branched alkyl group.[60]

Since the investigated cyclohexanes contain only one polar bond besides alkyl groups, it is not unexpected that the observed equilibria show generally minor deviations from values expected on the basis of single $\Delta G°$ values (Table VI). Exceptions are noted particularly for alcohols and amines, in which the OH and NH_2 $\Delta G°$ constants are altered by self association.

Experimental Section

^{13}C and ^1H NMR spectra at low temperature were recorded in PFT mode at 22.62 (21.14 kG) and 90 MHz, respectively, on a Bruker HX 90/Nicolet 1080 system using $CFCl_3$ for ^{19}F field-frequency lock and Me_4Si as an internal standard. The temperature was controlled with a Bruker BST 100/700 unit and found to be accurate to ±0.5 K using a "chemical shift" thermometric system.[61] Spectral width was 6000 Hz for ^{13}C NMR and 900 Hz for ^1H NMR, both at 8K/4K data points. Pulse angles of 30° (^{13}C NMR) could be used without additional delay after the FID scan (0.6 s). This procedure lead in ~1 M solutions to sufficient signal/noise ratios (>50) after 10 min accumulation time and was found to be more economical than applying 90° angles,[44a] while no differential T_1 effects were observable. Digitization errors were minimized by using peak widths extending over several computer addresses. This was achieved by staying in the region of not too slow of exchange or by measuring under nonoptimal field homogeneity.

Signal area ratios were determined by cutting and weighing paper copies and additionally in several cases by electronic integration or by complete line shape simulation. Overestimation of the larger peak, yielding too high of $\Delta G°$ values, can result from the neglect of the valley signal height between exchanging peaks. This systematical error, which increases with $\Delta G°$, must be minimized by the choice of not too fast of exchange or by line shape analysis and requires high signal to noise ratios. The accuracy obtainable is given in Tables V and VI; the reproducibility was checked with freshly prepared solutions of **1** (X = I, NCS, and OTs), yielding $\Delta\Delta G°$ deviations of 0.02, 0.002, and 0.012 kcal/mol, respectively.

Isomers of less than 5%, e.g., **7** (X = a-OH, a-OAc), were determined from the line shape at intermediate exchange rates. Since both $\Delta\nu$ and the exchange rate can be estimated from other cyclohexanes, the population is unambiguously deducible from the observed line shapes. In a typical experiment, 1% of the minor isomer produces for $\Delta\nu$ = 100 Hz and $k = 10^3$ s^{-1} an exchange broadening of 1.5 Hz at the "coalescence" point.

The preparation of materials that are not commercially available will be reported elsewhere.

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Registry No.—Methanesulfuric acid cyclohexyl ester, 66922-09-6; *N*-methylcyclohexylamine, 100-60-7; *N,N*-dimethylcyclohexylamine, 98-94-2; *N*-carboxaldehydecyclohexylamine, 766-93-8; cyclohexanecarboxyaldehyde, 2043-61-0; benzoylcyclohexane, 712-50-5; cyclohexanecarboxylic acid ethyl ester, 3289-28-9; cyclohexanemethanol, 100-49-2; *trans*-1-chloro-4-methylcyclohexane, 13064-82-9; *cis*-1-chloro-4-methylcyclohexane, 13064-81-8; *trans*-1-bromo-4-methylcyclohexane, 28046-91-5; *cis*-1-bromo-4-methylcyclohexane, 28046-90-4; *trans*-1-iodo-4-methylcyclohexane, 66922-10-9; *cis*-1-iodo-4-methylcyclohexane, 66922-11-0; *trans*-1-hydroxy-4-methylcyclohexane, 7731-29-5; *trans*-1-amino-4-methylcyclohexane, 2523-55-9; *trans*-1,4-dimethylcyclohexane, 2207-04-7; *cis*-1,4-dimethylcyclohexane, 624-29-3; methylcyclohexane, 108-87-2; 1-fluoro-1-methycyclohexane, 66922-12-1; 1-iodo-1-methycyclohexane, 40304-83-4; 1,1-dimethycyclohexane, 590-66-9.

Supplementary Material Available: ^{13}C NMR shifts of cyclohexane derivatives which are not reported in Tables I–IV (Tables Ia, Ib, and IIa) and Figure 6 (experimental and calculated line shape; example for possible error by valley signal height neglect) (6 pages). Ordering information is given on any current masthead page.

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