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Concerning the Generality of the Temperature Dependence of Carbon-13 Shieldings as a Probe for Conformational or Structural Equilibria

Joseph B. Lambert,*[1] Adelia R. Vagenas, and Sujata Somani

Contribution from the Department of Chemistry, Northwestern University, Evanston, Illinois 60201. *Received November 25, 1980*

Abstract: In order to assess the effect of the chair–twist equilibrium in six-membered rings on the temperature dependence of ^{13}C chemical shifts, we have examined a series of hydrocarbons and heterocycles with zero, one, or two geminal dimethyl groups. The temperature gradients of the chemical shifts, compared to that of internal Me_4Si, were curved for the quaternary carbons and were linear for all other carbons. These plots could be fitted to a best value of a free energy difference between two forms. The resulting free energy differences, however, bore no logical relationship to the degree of methylation, which should have determined the proportion of the twist form. Changes in solution density with temperature contribute to and may even dominate the temperature gradient of the shielding. These inherent contributions could not be factored out either by correcting for the temperature variation of Me_4Si or by making internal shift comparisons between carbons within the same molecule. Even the rigid 2,2-dimethyladamantane gave an artificial free energy difference by this analysis. Because the least-squares procedure requires very accurate data and because the inherent contributions vary from one carbon to the next in the same molecule, depending on the degree of substitution and the type of heterosubstitution, we conclude that calculation to correct for the inherent contribution is unrealistic. Consequently, the measurement of free energy differences from the temperature gradients of ^{13}C chemical shifts is not always reliable.

Carbon-13 chemical shifts exhibit a pronounced temperature dependence, ranging from about -200 to $+100 \times 10^{-4}$ ppm/K on the Me_4Si scale. In some cases, the shift gradient can be attributed to an increase with temperature of bond lengths or bond dipoles, caused by increased population of higher vibrational states.[2,3] In general, however, the shift gradient results from changes in the solution density with temperature. Increased density at lower temperatures creates stronger van der Waals interactions and hence deshielding (downfield shifts).[4]

In addition to these inherent contributions, the carbon-13 chemical shift can vary with temperature if the molecule exists in two or more interconverting forms with nonzero free energy differences. Under such circumstances, the observed chemical shift δ is the weighted average of the shifts of the contributors to the equilibrium (eq 1 for two forms). Rearrangement gives

$$\delta = p\delta_b + (1 - p)\delta_a \qquad (1)$$

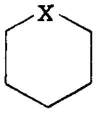
an expression (eq 2) for the observed chemical shift that is linear in p. Since p is related to the free energy difference ΔG between

$$\delta = \delta_a + (\delta_b - \delta_a)p \qquad (2)$$

forms ($K = p/(1 - p) = \exp(-\Delta G/RT)$), a least-squares fit of eq 2 can provide ΔG.

Applications to various nuclei have been known for some time,[5] but use of the effect with ^{13}C data is relatively recent. In particular, analysis of the ^{13}C shift gradient has provided approximate free energy differences for gauche/anti equilibria in substituted ethanes containing either polar or nonpolar groups.[2,3] Equilibria in carbonium ion systems have also been examined by this ^{13}C method.[6,7] In some of these cases, correction was made for the known dependence of the standard, Me_4Si, on temperature,[2] but in none has accurate allowance been possible for the inherent shift gradient. It must be assumed that contributions to the gradient from the conformational or structural equilibrium are larger than those from inherent factors. Since the inherent factors generally give rise to a linear temperature gradient, observation of pronounced curvature is particularly favorable in attempts to extract thermodynamic information.

In our studies of the conformational properties of saturated heterocycles,[8] we have prepared an extensive series of heterocyclohexanes (1) and of 3,3-dimethylheterocyclohexanes (2). Ex-



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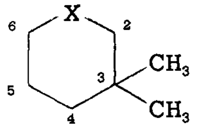

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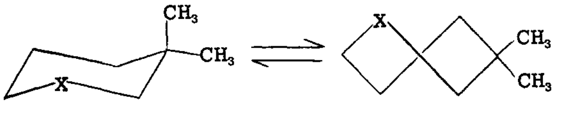
amination of the ^{13}C spectrum revealed a large temperature gradient for these systems. Although the gradient was linear for all carbons in the unmethylated systems and for the nonquaternary carbons in the 3,3-dimethyl systems, the gradient was quite nonlinear for the quaternary (3-position) carbons in **2**. The nonlinearity suggested to us contributions from conformational as well as inherent sources. For six-membered rings lacking an axial or equatorial bias, the most likely conformational equilibrium is between the chair and the twist boat form (eq 3). Except in



(3)

highly substituted systems,[9] the chair–twist equilibrium is well on the side of the chair form. Introduction of the geminal methyl groups in **2**, however, raises the energy of the chair form (one methyl must be axial) while affecting the twist form only modestly (the two methyls can be accommodated in the axis position). In this paper we analyze the ^{13}C chemical shift gradients of **1** and **2** in terms of the chair–twist equilibrium and inherent factors, and we reach general conclusions concerning the efficacy of this method.

Results

The heterocyclic compounds **1** ($X = O$, S, NH, NCH_3) and **2** ($X = O$, S, Te, NH, NCH_3) were available from previous

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[1] This work was supported by the National Science Foundation (Grant CHE79-05542) and by the National Institutes of Health (Grant R01 GM-26124).

[2] Schneider, H.-J.; Freitag, W. *J. Am. Chem. Soc.* **1976**, *98*, 478–481. Schneider, H.-J.; Freitag, W.; Hopper, V. *Org. Magn. Reson.* **1980**, *13*, 266–269.

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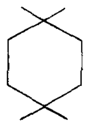
studies. For comparison with hydrocarbons and systems lacking conformational inhomogeneity, we also examined cyclohexane (**1**, X = CH_2), 1,1-dimethylcyclohexane (**2**, X = CH_2), 1,1,4,4-tetramethylcyclohexane (**3**), and 2,2-dimethyladamantane (**4**).



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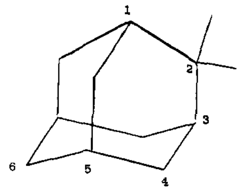

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The latter two materials were prepared by treatment of the analogous desmethyl ketone with trimethylaluminum.[10] Also included were the acyclic compounds 1,5-dibromopentane and 1,5-dibromo-3,3-dimethylpentane, available from the heterocyclic syntheses.

Carbon-13 spectra were examined from ambient temperatures (ca. 300 K) to below the coalescence temperature for ring reversal (ca. 180 K). Samples contained 5% solute, 25% $CDCl_3$, and 70% CH_2Cl_2. In the ^{13}C spectrum, only the exocyclic methyl group resonances are sensitive to the process of ring reversal, which alters the relationship between axial and equatorial substituents but not the overall ring structure. As a result, the methyl resonance exhibits decoalescence at low temperatures to two peaks, but the ring carbon resonances remain unsplit. The chemical shifts, measured vs. Me_4Si at 0 ppm as a function of temperature, have been recorded in detail elsewhere.[11]

In general, the ^{13}C chemical shifts relative to Me_4Si moved upfield with reduced temperature. Typical data are shown in Figure 1 for 3,3-dimethylpiperidine. The quaternary carbon shows a nonlinear response, and this result was general for all the heterocycles (see ref 11 for analogous plots for all other **2**). The methylene and methyl carbons exhibit linear behavior, with variable slope. For methyl, data were obtained above and below the coalescence temperature, with a gap in the data for the temperature range of coalescence.

This behavior was observed for all the systems, i.e., a nonlinear response from the quaternary carbon and a linear response from all other carbons. The slopes of these plots were always positive (upfield shift with lower temperature), with the exception of the carbons next to the heavy atoms Te and Br. These exceptions have been noted before.[2] Figure 2 illustrates the divergent behavior of the differently substituted carbons, including the standard nonlinear responses from the quaternary carbon. To test the sensitivity of the temperature gradient to solvent-solute interactions, we also carried out the appropriate experiments with 3,3-dimethyloxane in cyclopentane and with various hydrocarbons, e.g., 1,1-dimethylcyclohexane, in $CDCl_3/CH_2Cl_2$. The results were qualitatively the same.

Temperature gradients have generally been expressed in units of 10^{-4} ppm/K, with a positive number indicating an upfield shift with reduced temperature. The gradients were calculated from a linear least-squares fit of the plot of chemical shift vs. temperature. Correlation coefficients were invariably larger than 0.99, except for the quaternary carbons. Table I lists the gradients for the systems studied.

Because the chemical shift of the internal standard, Me_4Si, also varies with temperature, Table I and the figures are somewhat misleading. All chemical shifts were calculated in the second place with a correction for this variation, according to Jameson's equation, $\delta(T) - \delta(300) = -0.013\,191(T - 300) - 1.1907 \times 10^{-5}(T - 300)^2$(ppm).[12] The resulting chemical shifts are relative to a temperature invariant standard at 300 K. Application of this equation reveals the normal downfield effect as the temperature

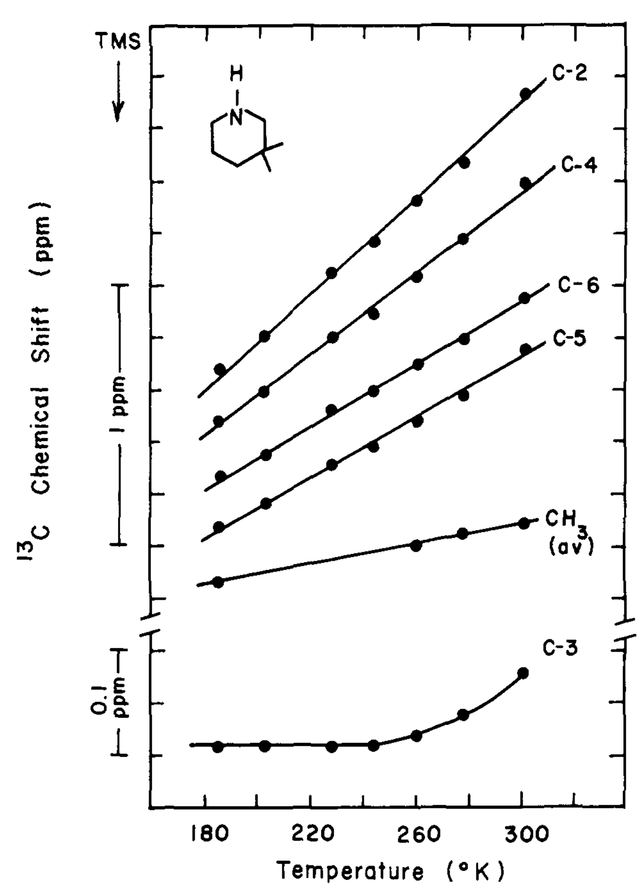

Figure 1. The carbon-13 chemical shift (δ) relative to uncorrected Me_4Si as a function of temperature for 3,3-dimethylpiperidine (**2**, X = NH). The δ scale increases from the bottom to the top of the plot.

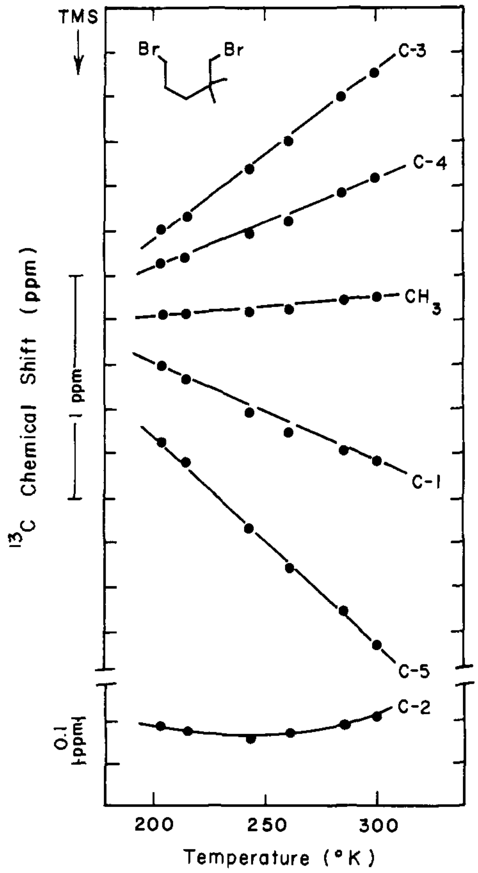

Figure 2. The carbon-13 chemical shift (δ) relative to uncorrected Me_4Si as a function of temperature for 1,5-dibromo-2,2-dimethylpentane. The δ scale increases from the bottom to the top of the plot.

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[12] This relationship is due to C. J. Jameson and has been reported by: Jackowski, K.; Raynes, W. T. *J. Chem. Soc., Chem. Commun.* **1979**, 863-864.

Table I. Carbon-13 Chemical Shift-Temperature Gradients (10^{-4} ppm/K)[a]

	C_1	C_2	C_3	C_4	C_5	C_6	CH_3[b]	CH_3[c]
2, X = O[d]		44	*e*	71	42	11	15	
2, X = O[f]		45	*e*	47	26	17	*g*	
2, X = S		60	*e*	71	47	26	14	
2, X = Te		−48	*e*	75	48	−88	19	
2, X = NH		91	*e*	78	58	59	19	
2, X = NCH_3		57	*e*	78	40	32	11	0
2, X = CH_2[h]	32	57	*e*	57	32	26	10	
1, X = O		10	36	35	36	10		
1, X = S		31	38	44	38	31		
1, X = NH[i]		42	64	33	64	42		
1, X = NCH_3		42	28	35	28	35		
1, X = CH_2	32	32	32	32	32	32		
3[j]	0	68	68	0				10
4[k,l]	78	54	78	69	67	76		
m, n		−133	27	23	27	−133		
o, h		−45	2	74	40	−94	8	

[a] Relative to uncorrected Me_4Si. [b] Methyl at the 3-position. [c] Methyl at the 1-position. [d] Solvent is 25% $CDCl_3$ and 70% CH_2Cl_2 unless otherwise noted. [e] Curved response with near zero slope. [f] Solvent cyclopentane. [g] Only two data points obtained. [h] The carbons are numbered arbitrarily with the methyls at the 3-position. [i] 25% substrate in 25% $CDCl_3$ and 50% CH_2Cl_2. [j] 1,1,4,4-Tetramethylcyclohexane. [k] 2,2-Dimethyladamantane. [l] Methyl is at the 2-position; numbering of other positions is given in structure 4; methyl and C_5 overlap. [m] 1,5-Dibromopentane. [n] Arbitrary numbering to conform to 1 and 2. [o] 1,5-Dibromo-3,3-dimethylpentane.

Table II. Free Energy Differences (cal/mol) from Uncorrected Chemical Shifts

	C_1	C_2	C_3	C_4	C_5	C_6	CH_3[a]
2, X = O[b]		1100	*c*	1050	1100	1800	
2, X = O[d]		1550	*c*	1900	2250	2000	
2, X = S		1550	*c*	1400	1500	1900	
2, X = Te		450	*c*	1050	900	700	
2, X = NH		1350	*c*	1400	1400	1200	
2, X = NCH_3		1550	3350	1450	1750	1400	*c*
2, X = CH_2[e]	1150	1750	*c*	1750	1150	1550	
1, X = O		2000	1500	1200	1500	2000	
1, X = S		2000	1450	1350	1450	2000	
1, X = NH[f]		2000	1600	2000	1600	2000	
1, X = NCH_3		1150	1450	1500	1450	1150	*c*
1, X = CH_2	850	850	850	850	850	850	
3[g]	*c*	1150	1150	*c*			
4[h]	850	3800	850	1800		*c*	

[a] Methyl at the 1-position. [b] Solvent is 25% $CDCl_3$ and 70% CH_2Cl_2 unless otherwise noted. [c] Not determined (50–4000 cal/mol fitted almost equally well). [d] Cyclopentane solvent. [e] The carbons are numbered arbitrarily with the methyls at the 3-position. [f] 25% $CDCl_3$ and 50% CH_2Cl_2. [g] 1,1,4,4-Tetramethylcyclohexane. [h] 2,2-Dimethyladamantane.

Table III. Free Energy Differences (cal/mol) from Chemical Shifts Corrected for Temperature Variance of Me_4Si

	C_1	C_2	C_3	C_4	C_5	C_6	CH_3[a]
2, X = O[a]		1350	1100	1700	1350	1200	
2, X = O[a]		1300	1150	1100	1200	1300	
2, X = S		1050	1000	1100	1150	1100	
2, X = Te		1050	1100	1700	1550	1050	
2, X = NH		1200	1150	1200	1250	1400	
2, X = NCH_3		1300	1200	1250	1250	1400	1400
2, X = CH_2	1450	950	1250	950	1450	1300	
1, X = O		1350	1450	1450	1450	1350	
1, X = S		1150	1250	1300	1250	1150	
1, X = NH		950	1000	1050	1000	950	
1, X = NCH_3		1350	1200	1200	1200	1350	1400
1, X = CH_2	1600	1600	1600	1600	1600	1600	
3[a]	1300	1850	1850	1300			
4[a]	3500	500	3500	1700			

[a] See analogous footnotes in Table II.

Table IV. Free Energy Differences (cal/mol) from Chemical Shift Differences with Respect to C_5

	C_1	C_2	C_3	C_4	C_5	C_6	CH_3[a]
2, X = O[a]		750	900	1550		2750	
2, X = O[a]		1650	700	900		850	
2, X = S		1650	800	1150		950	
2, X = Te		700	400	1450		750	
2, X = NH		1250	1050	1150			
2, X = NCH_3		850	1000	1200		3200	1750
2, X = CH_2		1500	1300	1500		3200	
1, X = O		900		1150		900	
1, X = S				700			
1, X = NH[a]		850		1150		850	
1, X = NCH_3		700		1800		700	2200
3[a]	1000			1000			

[a] See analogous footnotes in Table II.

is reduced (negative gradients). The upfield shifts of Table I and the figures result from the fact that these carbons are less sensitive than those of Me_4Si to temperature. For example, C_2 of **2** (X = NH) has a gradient from Figure 1 of 91, but after correction for Me_4Si the gradient becomes −28; C_4 goes from 78 to −40, C_5 from 58 to −61, CH_3 from 19 to −100, and so on. Thus, commonly reported shift gradients are to a large extent artifacts of the choice of standard. The higher sensitivity of Me_4Si to van der Waals effects is not unexpected.

If the dominant cause of the temperature variation were an equilibrium between conformational forms, the free energy difference could be calculated by the best fit to eq 2. Table II gives the best fits to the chemical shifts uncorrected for the temperature dependence of Me_4Si, and Table III gives the same results for the corrected chemical shifts. An approach that avoids the referencing problem entirely is to analyze the temperature dependence of the chemical shift difference between resonances within the same molecule. We calculated the chemical shifts of all the carbons in **2** with respect to C_5 and in **1** with respect to $C_{3,5}$. These chemical shift differences do not depend on the properties of Me_4Si. Their temperature dependence was analyzed as above and the resulting free energy differences are found in Table IV.

Discussion

The use of temperature-dependent chemical shifts to calculate conformational free energy differences has been widespread and longstanding. Mislow and co-workers referred to it as the Wood–Fickett–Kirkwood (WFK) method.[13] They were critical of its reliability unless both chemical shift and temperature data were extremely accurate. Thus it is a sine qua non of the method in the current context either that there be no source of chemical shift variation except the conformational equilibrium or that an extremely accurate method exist for allowance for other factors. Let us assume the validity of this condition and examine our

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[13] Joshua, H.; Gans, R.; Mislow, K. *J. Am. Chem. Soc.* **1968**, *90*, 4884–4892. Gans, R. Ph.D. Dissertation, Princeton University, 1968. Wood, W. W.; Fickett, W.; Kirkwood, J. G. *J. Chem. Phys.* **1952**, *20*, 561–568.

calculated free energy differences.

The thesis of this work is that introduction of a pair of methyl groups at C_3 will lower the energy of the twist form relative to the chair form. Thus, in general, the free energy difference for **2** should be lower than that for **1**. Introduction of another pair of methyls on the axis of molecular symmetry should further reduce the energy of the twist form, as in 1,1,4,4-tetramethylcyclohexane (**3**). Rigid molecules such as 2,2-dimethyladamantane (**4**) should exhibit an infinitely large free energy difference, since a second conformer is not possible.

Most workers have employed chemical shifts measured directly against Me_4Si, without correction for the temperature variation of the standard.[3,6,7] Our analogous free energy calculations are found in Table II. None of the expected trends is observed. If anything, the unsubstituted **1** shows a larger free energy difference than **2**, and the quadruply substituted **3** shows a comparable free energy difference to **2**. Worse, the adamantane **4** appears to respond to the analysis as if it existed in two forms. Finally, the data from carbon to carbon within a single molecule are not consistent. For example, the free energy differences for 3,3-dimethyloxane vary from 1050 to 1800 cal/mol, those for oxane vary from 1200 to 2000 cal/mol, and those for the adamantane vary from 850 to 3800 cal/mol. The shift data for the quaternary carbons failed to give a least-squares minimum, so that the entire range (50–4000 cal/mol) was equally good. Thus the data are not consistent internally or with respect to expected substituent effects.

These defects in the method might be the result of the failure to allow for the temperature dependence of the standard. One group has strongly recommended such corrections.[2] The free energy differences from the corrected chemical shifts are found in Table III. Indeed, much more consistent numbers result. For both the methylated series **2** and the unmethylated series **1**, the typical range for all carbon atoms within a molecule is only about 100–200 cal/mol, with three exceptions, and the quaternary carbons give the same minimum. Unfortunately, the unmethylated compounds **1** including cyclohexane exhibit essentially the same free energy differences (average 1300 cal/mol) as the methylated compounds **2** (average 1230). The series cyclohexane, 1,1-dimethylcyclohexane, 1,1,4,4-tetramethylcyclohexane shows the trend 1600, 1255 (average), and 1575 (average) cal/mol. The adamantane **4** still shows a finite value, 2000 (weighted average) cal/mol. Perusal of the table in fact suggests that all of the carbons give rather similar free energy differences. The correction for the Me_4Si gradient, which is about -120×-10^{-4} ppm/K, appears to have dominated the calculation and imposed a homogeneity on the results. The larger van der Waals interactions for Me_4Si have overcorrected the shifts. Despite their apparent internal consistency, the free energy differences from the corrected chemical shift differences do not appear to have validity.

To avoid the problem of the standard, we can carry out the calculation on chemical shifts measured relative to a specific carbon within the same molecule. Because the different carbons have distinct chemical shifts in both conformers, the difference between their average shifts will show a temperature dependence. This method was very effective for geminal difluorides, CF_2.[5] In the absence of a conformational effect and provided that the inherent effect is either zero or equivalent at the two carbons, subtraction of the shifts should yield a constant value. Variations could then be attributed to equilibrium changes. In fact the subtracted values are quite temperature dependent, and the resulting free energies are given in Table IV. Suffice it to say that the values are neither internally nor externally consistent.

We are forced to conclude that analysis of the temperature dependence of ^{13}C chemical shifts in this context does not provide accurate free energy differences. The least-squares method does provide minima, so that extreme caution should be observed in such a situation. For example, analysis of the data for 1,1,4,4-tetramethylcyclohexane without reference to cyclohexane or 1,1-dimethylcyclohexane would have provided a tempting but entirely false result of 1200–1800 cal/mol (Tables II and III). It is quite possible that in some instances the effect caused by the conformational or structural equilibrium entirely dominates the inherent effect, so that the analysis becomes valid.[2] Such a condition, however, would have to be demonstrated in every case. We conclude that in methylated cyclohexanes and heterocyclohexanes the inherent effects, caused probably by variation of the solution density with temperature, are too large for the WFK method,[13] which requires that the temperature variation come only from the equilibrium shift. We are not in a position to question literature values of ΔG based on this method,[2,3,6,7] as these ^{13}C shifts may indeed be dominated by the equilibrium. Because the inherent effect is so large in general for ^{13}C, we do, however, urge caution in applying the method in any system.

Is it possible to allow accurately for the inherent effect? Such a process would involve finding two carbons with identical inherent effects, subtracting the shifts as we did for Table IV, and analyzing the temperature dependence of the residue. The method was not successful in Table IV, but it might be in other systems, as in the ^{19}F case.[5] To consider which systems might be favorable, it is necessary to examine structural effects on the inherent variation. Some data are already in the literature. Cheng and Bovey[3] found that in normal alkanes α-alkylation increases the gradient by 16 $\times 10^{-4}$ ppm/K, β-substitution by 12, γ-substitution by -15, and so on. Schneider and co-workers examined the effect of polar substituents on the gradient for the α-, β-, and γ-carbons in neopentyl systems, $(CH_3)_3CCH_2X$.[2]

Examination of our data provides further insight. Comparison of series **1** with series **2** gives the effect of geminal dimethyl substitution. Comparison of series **2** with 1,1-dimethylcyclohexane and of series **1** with cyclohexane gives the heteroatom effect. For example, the geminal dimethyl group clearly increases the gradient for an α-carbon. Within series **2**, the increase may be calculated by subtracting the gradients of C_2 and C_6, which are equivalently affected by the heteroatom. The respective differences for O, S, Te, NH, NCH_3, and CH_2 are 33, 34, 40, 31, 25, and 31 $\times 10^{-4}$ ppm/K, or an average of 32×10^{-4} ppm/K. Alternatively, the C_2 and C_4 gradients for the dimethyl series **2** could be subtracted from the analogous gradients for the unmethylated series **1**. The range is large ($(15–48) \times 10^{-4}$ ppm/K), but the average is still 33×10^{-4} ppm/K. Although introduction of a geminal pair of methyl groups augments the gradient of the α-carbons by about 32×10^{-4} ppm/K on the average, there is still considerable structural variation throughout the series. Thus it would be unwise to attempt to allow for methylation by an arbitrary subtraction of 32 from the gradient in order to provide an internal calibration during the calculation for free energy differences. Analogous effects on carbons β or γ to the quaternary carbon are smaller, ranging from -10 to $+17 \times 10^{-4}$ ppm/K.

The effect of the heteroatom on the gradient can be calculated in a similar fashion. The value for cyclohexane, 32×10^{-4} ppm/K, may be subtracting from the C_2, C_6 value for the unmethylated series **2**, to give the following effects of a heteroatom on the gradient of the α-carbon: O, -22; S, -1; NH, 10; NCH_3, 2. The heteroatom also has an effect on the β-carbon (O, 4; S, 6; NH, 32; NCH_3, -4) and on the γ-carbon (O, 3; S, 12; NH, 1; NCH_3, 2). Of these, the only significant effect is at the carbons that are β to NH. Within the dimethyl series, the calculation for the α effect is carried out by subtracting 26 (the value for the C_6 gradient in 1,1-dimethylcyclohexane) from the C_6 gradient. Use of C_6 minimizes any effect from the quaternary center. The resulting α effects are as follows: O, -15; S, 0; Te, -114; NH, 33; NCH_3, 6. Thus the numbers are similar for **1** and **2**. For the β effect, the subtractive factor is 32, and the resulting changes are as follows: O, 10; S, 15; Te, 16; NH, 26; NCH_3, 8. The γ calculation is probably not reliable because it would involve a carbon α to the quaternary center. It is noteworthy that all the β and γ effects are small except that for a β-NH group. The fact might be dismissed as an artifact, except that it appears in both the methylated (26) and the unmethylated (32) series.

The heteroatom effects have been discussed by Schneider et al.,[2] and our results are entirely in agreement with theirs. They observe small β and γ effects. The largest α effects are observed for the most polarizable atoms, such as Te, and can be explained in terms of larger van der Waals interactions. The important conclusion for our analysis is that heteroatom effects propagate out to at least the γ-position and vary with the distance. *Thus the inherent effect varies from atom to atom as a function of substitution.* This variation is responsible for the lack of reliability of the results in Table IV, in which C_5 was used as an internal chemical shift standard.

Summary and Conclusions

We have found that the chair–twist equilibrium is not amenable to analysis by the temperature dependence of ^{13}C chemical shifts. Although it is quite likely that a change in the equilibrium does contribute to the variation of the shift with temperature, the conformational factor is accompanied by or even overwhelmed by intrinsic effects, such as variation of solution density with temperature. Our approach was to use increasing degrees of methylation to shift the equilibrium toward the side of the twist form. For this purpose we used a series of heterocyclohexanes (**1**) (plus the parent hydrocarbon), their 3,3-dimethyl derivatives (**2**), and 1,1,4,4-tetramethylcyclohexane (**3**). The chemical shift data were analyzed in three ways. Chemical shifts measured relative to Me_4Si failed to give conformational free energy differences that exhibited the expected trend of an increased proportion of the twist form with additional methyl substitution. Moreover, the free energy differences varied according to which carbon shift was used for the calculation. Adjustment of all the shifts for the temperature dependence of the standard, Me_4Si, yielded free energy differences that were internally consistent for a given molecule but that were rather similar for all systems examined. The adjustment for the standard apparently introduces a systematic factor that dominates the calculation. Measurement of the shifts relative to a specific carbon within the same molecule (C_5 in our case), to avoid calibration of the standard, provided results that were neither internally consistent nor in agreement with methylation expectations. Both cyclohexane itself, which should have a large free energy difference, and 2,2-dimethyladamantane, which should have an infinite difference, gave values similar to those for the remaining systems. The internal allowance for intrinsic effects apparently is systematically in error.

We conclude that, despite obtaining convergent results from the calculations for free energy differences, the values have no significance in the conformational context. Similar results were obtained for chemical shifts that exhibited either linear or curved (C_3) gradients with temperature. Apparently the fact of a curved plot by itself does not imply that the equilibrium dominates the chemical shift gradient. For all the carbons in our systems, the inherent factors must contribute sufficiently to throw off the free energy calculation. It has been pointed out that this type of calculation is extremely sensitive to the accuracy of the data.[13] Thus it stands to reason that the existence of a significant factor other than the equilibrium shift with temperature would introduce a possibly fatal systematic error into the calculation. It may be that in some cases other than those studied here, the inherent factors are small, compared to the equilibrium shift, but this conditions would have to be demonstrated. It seems unlikely that an allowance for the inherent factors could be easily factored into the calculation. Introduction of either alkyl groups or heteroatoms influences the temperature gradient several carbons removed from the point of substitution, and the exact factor varies slightly from atom to atom and system to system. For these reasons we caution against the use of this method in the calculation of free energy differences from ^{13}C chemical shifts unless solid evidence can be presented that the inherent factors either are small or have been accurately subtracted out.

The WFK method can be used to provide free energy differences from a wide variety of data other than ^{13}C chemical shifts (NMR coupling constants, chemical shifts other than ^{13}C, dipole moments, rotational strengths, and so on). The conclusions we reach in this study do not necessarily apply to these other techniques, which may not have large temperature gradients caused by inherent sources. In these other contexts, the WFK method can be a unique and accurate approach to the determination of thermodynamic quantities in rapidly equilibrating systems.

Experimental Section

Carbon-13 spectra were measured at 20 MHz with a temperature-controlled Varian CFT-20 NMR spectrometer, operating in the pulsed Fourier transform mode with proton decoupling. From 800 to 2000 scans were routinely accumulated. Chemical shifts were calculated in parts per million downfield from tetramethylsilane. Variable-temperature ^{13}C spectra were measured on 5% samples in a 25% $CDCl_3$/70% CH_2Cl_2 solvent system, with a trace of internal Me_4Si added for reference. Probe temperatures were measured with an Omega Model 175 thermocouple inserted into a sample tube containing 30% $CDCl_3$/70% CH_2Cl_2. The reported temperatures were obtained by averaging the readings before and after the accumulation of data. The field/frequency stabilization of the spectrometer was obtained by locking on the ^2H signal of $CDCl_3$. The unmethylated heterocycles **1** were commercially available, and the geminally methylated heterocycles **2** were available from another study.

2,2-Dimethyladamantane (4).[10] Into an evacuated 250-mL pyrolysis tube containing 2.5 g (16.7 mmol) of adamantanone (Aldrich) was added 8.25 mL (16.7 mmol) of trimethylaluminum (2 M in toluene) via syringe. (*Caution*! $Al(CH_3)_3$ is pyrophoric; handle and store under N_2.) The pyrolysis tube was sealed under vacuum and heated in a tube oven at 150–170 °C for 24 h. After being cooled in dry ice/acetone, the tube was cautiously opened and the contents were hydrolyzed with dilute HCl. The mixture was extracted with ethyl ether and pentane. The pentane extracts were dried (Na_2SO_4) and evaporated. The product was further purified by preparative TLC to afford white crystals (1.89 g, 69%), mp 143–145 °C (lit.[14] 141–142 °C).

1,1,4,4-Tetramethylcyclohexane (3).[10] Into an evacuated 250-mL pyrolysis tube containing 3.0 g (23.8 mmol) of 4,4-dimethylcyclohexanone was added 11.8 mL (23.8 mmol) of trimethylaluminum (2 M in toluene) via syringe. The tube was sealed and heated in a tube oven at 150–160 °C for 20 h. The pyrolysis tube was cooled in a dry ice/acetone bath, and the contents were hydrolyzed with dilute HCl. The organic layer was separated, and the aqueous layer was extracted with 4 × 3 mL of pentane. The organic extracts were dried (Na_2SO_4) and distilled to give 1.6 g (48%) of **3**: bp 147–151 °C (lit.[15] 146–148 °C (750mmHg)); ^1H NMR δ 0.86 (6, s, CH_3), 1.24 (4, s, CH_2).

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