Conformational analysis. Part 36.[1] A variable temperature ^{13}C NMR study of conformational equilibria in methyl substituted cycloalkanes

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The conformational equilibria in six methylcycloalkanes have been investigated using the temperature dependence of the ^{13}C chemical shifts at temperatures above the coalescence point. Using conformationally homogeneous compounds as standards the temperature dependence was analysed to give the conformer energy differences ΔH (ax–eq). These were for methylcyclohexane 1.92 kcal mol^{-1}, 2- and 3-methylcyclohexanone 1.58 and 1.35 kcal mol^{-1}, 3-methyltetrahydropyran 1.50 kcal mol^{-1} and 2- and 4-methylpiperidine >2.6 and 2.30 kcal mol^{-1}. These values are compared with previous literature values and theoretical values from molecular mechanics and *ab initio* calculations. They are in very good agreement with previous literature values and the *ab initio* values, but the values from MM calculations show larger differences. The only exceptional case is 2-methylcyclohexanone in which the *ab initio* value of 2.38 kcal mol^{-1} is much larger than the energy difference in chloroform solution determined here (1.58 kcal mol^{-1}) which is in good agreement with previous literature data in solution. Sterically hindered solvation in the equatorial conformer is the most likely cause of this difference. It is concluded that this technique represents a novel and useful approach to conformational analysis.

Introduction

^{13}C NMR spectroscopy has proved a very powerful technique for identification purposes and stereochemical analysis in organic chemistry.[2] In the field of conformational analysis, the major use of ^{13}C spectroscopy has been to derive the energies of activation of numerous conformational equilibria by observing the temperature at which the peaks of the separate conformers coalesce.[3] Also, if sufficiently low temperatures can be achieved the conformer energy differences may be obtained by simple integration.

Few attempts have been made to obtain conformational information from the average ^{13}C chemical shifts observed at high temperatures, where the conformational equilibrium is fast on the NMR time scale. Yet this is a necessity both for molecules in which the interconversion barrier is too low to observe the individual conformers (*e.g.* cyclohexanones), and in many solvents (D_2O, DMSO, benzene, CCl_4) where the solvent freezing point is too high to detect coalescence for most conformational equilibria.

In this paper an approach is presented in which the conformer energies are obtained directly from a curve fitting analysis of the ^{13}C chemical shifts as a function of temperature. The chemical shift of any given carbon of a molecule which is rapidly interconverting between different conformers is a population weighted average of the carbon chemical shifts of the individual conformers. This provides the basis for the determination of the conformer populations through the use of ^{13}C chemical shifts. However, it is often the case that the individual conformer shifts are unknown but are estimated using substituent chemical shifts (SCS). The accuracy of the derived conformer distribution is then much more dependent on how well these SCS reproduce the true chemical shifts of the contributing conformers than on the accuracy of the observed chemical shift itself. The latter can easily be accurate to 0.01 ppm while the estimated shifts have much larger uncertainties.

As the temperature of the sample decreases the population of the more stable conformer increases causing the carbon chemical shifts to vary accordingly. Although these populations may vary only slightly due to temperature effects, the high accuracy of the chemical shift measurements allows the detection of these changes. For instance, a carbon atom in a 1,3 relationship to a methyl substituent in a six-membered ring (gamma position) may show a difference in chemical shifts between conformers of 5–6 ppm.[2] If the conformer populations were to vary by 1%, the chemical shift would vary by 0.05–0.06 ppm. This is easily detectable as an accuracy of 0.01 ppm is not difficult to achieve.

In a pioneering study Schneider and Freitag[4] measured the variation of ^{13}C chemical shifts with temperature for a number of cyclic and alicyclic hydrocarbons. They found that for compounds which exist in a single conformation the temperature variation of the ^{13}C chemical shifts was accurately linear over the temperature range studied. They also found that in conformationally inhomogeneous hydrocarbons the ^{13}C shifts of all carbon atoms not involved in the conformational equilibria were linearly deshielded with increasing temperature, but those carbon atoms which participated in *gauche–trans* conformational equilibria gave a marked nonlinear upfield shift. They described a curve fitting analysis for *n*-butane which gave a conformational energy difference of 0.3–0.7 kcal mol^{-1}.† However since this pioneering study there has not been any other example of the use of this technique in conformational analysis.

In this paper we extend this approach to analyse the conformational equilibria in methylcyclohexane, 2- and 3-methylcyclohexanone, 3-methyltetrahydropyran and 2- and 4-methylpiperidine. We show that this technique is capable of obtaining accurate values of the conformer free energy differences in these systems.

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† 1 kcal mol^{-1} = 4.184 kJ mol^{-1}.

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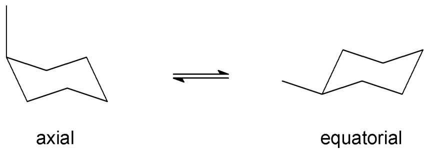

Fig. 1 The conformational equilibrium of methylcyclohexane.

Theoretical

The methyl derivatives considered interconvert between two chair conformations (Fig. 1) and the conformational equilibrium is given by eqn. (1) where n_{ax} and n_{eq} are the mole

$$\Delta G = -RT \ln (n_{eq}/n_{ax}) \qquad (1)$$

fractions of the axial and equatorial conformers, respectively. At any temperature above coalescence the conformers are in rapid equilibrium and the observed chemical shift for the carbon atom (δ_{obs}) is given by eqn. (2), where δ_{ax} and δ_{eq} are the

$$\delta_{obs} = n_{ax}\delta_{ax} + n_{eq}\delta_{eq} \qquad (2)$$

chemical shifts of that carbon atom in the axial and equatorial conformers, respectively.

Following Schneider and Freitag[4] the intrinsic temperature dependence of the carbon chemical shifts in the two conformers can be accounted for by a linear equation [eqn. (3)]. The

$$\begin{aligned}\delta_{ax} &= a + bT \\ \delta_{eq} &= c + bT\end{aligned} \qquad (3)$$

temperature gradient is taken from a reference molecule which does not undergo changes in chemical shifts related to conformational inversions. For example, the gradients for C3 of the two conformers of methylcyclohexane (Fig. 1) are considered to be the same as that of cyclohexane. Combining eqns. (1), (2) and (3) yields eqn. (4).

$$\delta_{obs} = \{(a - c)/(1 + \exp(-\Delta H/RT + \Delta S/R))\} + c + bT \qquad (4)$$

The curve fitting of the experimental points (δ_{obs}, T) into eqn. (4) provides values for the four unknowns, which are the intercepts a and c, and ΔH and ΔS.

Eliel *et al.* note that due to the symmetrical nature of the methyl group, the difference in entropy (ΔS) between the axial and equatorial conformers is very small.[3] An upper limit of ±0.05 cal mol^{-1} K^{-1} was adopted in our calculations which therefore essentially determines the three unknowns a, c and ΔH.

The method relies on the variation of carbon chemical shifts due to variations of the mole fraction of conformers with temperature. Thus the analysis is most accurate for carbons that show a large difference in chemical shifts between the conformers. For the methyl substituent under study, the gamma carbon is therefore a good choice. The method also shares the limitations of most other methods of conformational analysis regarding the difficulty of analysing a very biased system. In this case too high a value of ΔH cannot be treated properly because the variation of conformers mole fraction (Δn) is minimal. This variation can also be very small if ΔH approaches zero.

Experimental

^{13}C NMR spectra of *ca.* 40 mg ml^{-1} solutions in $CDCl_3$ referenced to TMS were obtained on a Bruker AMX 400 spectrometer operating at 100.63 MHz for carbon. Typical conditions were as follows: 600 transients, 1 s pulse delay, spectra width 10 869 Hz (for carbonyl compounds 26 000 Hz) with 32 k data points zero filled to 128 k for a 0.17 Hz digital resolution (0.4 for carbonyl compounds). The probe temperature was checked against a thermocouple and was accurate to ±2 K.

Compounds **1**–**4**, **6**, **8**–**13** were commercially available from Aldrich. Compound **5** was prepared according to an adaptation of the method of Langhals and Langhals[5] as follows: solid KOH (11.2 g, 0.2 mol) and 4-methylcyclohexanone (5.60 g, 0.05 mol) were added to 80 mL of DMSO in a three-necked flask equipped with a condenser, addition funnel and magnetic stirrer. Iodomethane (3.7 mL, 0.06 mol) was added under stirring to the reaction flask. The temperature was kept at 40–50 °C for 3 hours. The reaction mixture was poured into 250 g of ice–water and the product extracted with hexane. After removal of the solvent the product was distilled through a Vigreux column and a fraction collected at 80 °C/20 mmHg containing 3.1 g of *cis*-2,4-dimethylcyclohexanone together with a small amount of starting material.

Compound **7** and its *trans* isomer were obtained by the dichromate oxidation[6] of 3,5-dimethylcyclohexanol (Aldrich).

The molecular mechanics calculations were performed using PC Model v.7[7] and the DFT calculations using Gaussian 98.[8] Density function theory (DFT) was used with the B3LYP/6-31G** basis set in the Gaussian 98 program.

The curve fitting program used was developed in C++ and is based on the plot of ln k *versus* $1/T$. It systematically generates values for a and c, reads the value of b along with the experimental data and calculates the linear correlation coefficient (r) between $\ln((a + bT - \delta_{obs})/(\delta_{obs} - c - bT))$ and $1/T$. Whenever r is greater than 0.99, ΔS and ΔH are calculated from the intercept and slope of the plot, respectively. If the calculated ΔS is smaller than 0.05 cal mol^{-1} K^{-1} the parameters are inserted into eqn. (4) and the chemical shifts are calculated. If the experimental and calculated shifts for every point do not differ by more than 0.013 ppm a, c and ΔH values are saved.

Results

Reference compounds

The ^{13}C NMR spectra of the following reference compounds (Fig. 2) were obtained in $CDCl_3$ solutions: *trans*-1,4-dimethylcyclohexane (**1**), cyclohexanone (**2**), tetrahydropyran (**3**), cyclohexane (**4**), *cis*-2,4-dimethylcyclohexanone (**5**), piperidine (**6**), *cis*-3,5-dimethylcyclohexanone (**7**). These compounds have been chosen as references from which the parameters b are taken because they either are fixed in a single chair conformation (**1**, **5**, **7**) or show ring inversion (**2**, **3**, **4**, **6**) but with two equivalent chair conformations. Thus any temperature dependence of the carbon chemical shifts of these compounds must be solely due to the linear variation with temperature [eqn. (5)].

$$\delta_{obs} = a + bT \qquad (5)$$

Also the carbon skeletons are similar to the conformationally mobile compounds under study.

Table 1 presents the intercepts a, the slopes b, the correlation coefficients r, the standard deviations and the number of points fitted for the linear regression analysis of the observed chemical shifts of the various carbons *versus* temperature, with the temperature range considered. It is noteworthy that the correlation coefficients, r, are >0.99 in most cases and the standard deviations are smaller than the experimental accuracy of 0.01 ppm supporting the accuracy of eqn. (5). The lower values of r occur for those carbon atoms with a small temperature gradient. The extreme case is that of C6 of **5** which is nearly temperature independent and has an r-value of 0.83.

Table 1 Linear regression analysis of the ^{13}C chemical shifts of the reference compounds in $CDCl_3$ solution

Compd.[a]	Carbon	a (ppm)	b (10^4 ppm K^{-1})	Correlation coefficient r	Stan. devn. (ppm)	Number of points
1[b]	1,4	31.25	41.9	0.9997	0.004	5
	2,3,5,6	33.62	60.7	0.9995	0.007	5
	7,8	23.18	−14.6	0.9927	0.006	5
2	2,6	42.19	−6.5	0.9800	0.004	10
	3,5[c]	26.52	17.7	0.9960	0.003	6
	4	23.75	42.0	0.9988	0.007	10
3	2,6	68.72	14.0	0.9820	0.011	6
	3,5	25.22	51.7	0.9980	0.011	6
	4	22.05	52.7	0.9994	0.008	6
4[d]	All	25.78	39.3	0.9980	0.006	4
5	1	222.11	−284.0	0.9988	0.060	6
	2[e]	43.65	23.0	0.9910	0.013	6
	3	42.27	76.1	0.9997	0.008	6
	4	30.47	54.3	0.9999	0.003	6
	5	34.80	38.1	0.9995	0.005	6
	6	41.22	1.8	0.8300	0.005	6
	7	14.94	−14.9	0.9910	0.008	6
	8	21.35	−2.0	0.9160	0.004	6
6	2,6	45.98	48.7	0.9987	0.010	8
	3,5	25.03	72.7	0.9987	0.015	8
	4	23.82	43.9	0.9988	0.009	8
7	2,6	48.75	20.0	0.9870	0.014	6
	3,5	32.52	23.9	0.9995	0.003	6
	4	39.90	93.0	0.9999	0.004	6
	1	219.85	−277.0	0.9995	0.038	6
	7,8	22.62	−7.3	0.9780	0.006	6

[a] Temperature range: 223–323 K, except where indicated. [b] 210–283 K. [c] 233–283 K. [d] 243–288 K. [e] Exactly described by $\delta C2 = 44.41 - 0.00331T + 10^{-5}T^2$.

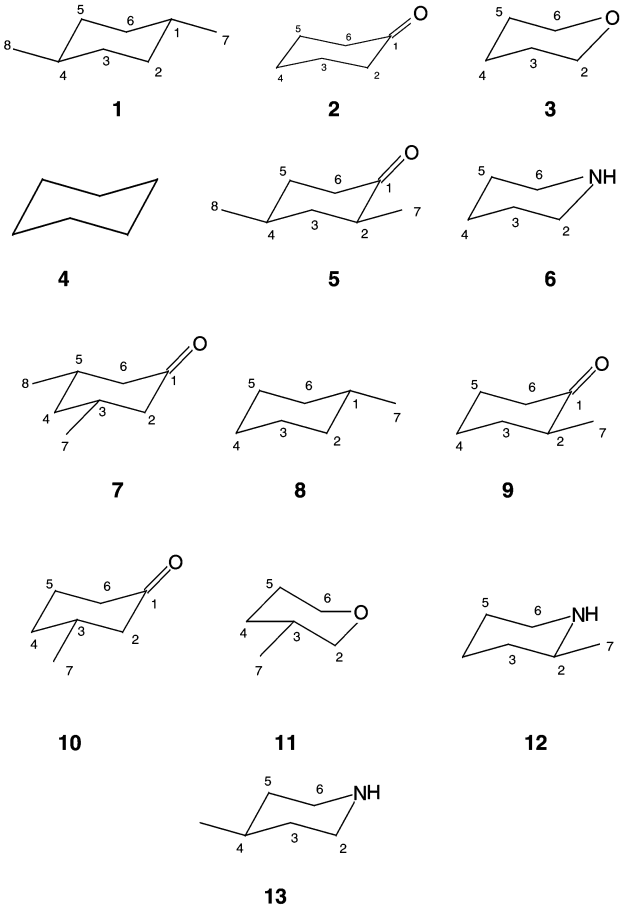

Fig. 2 Structures of compounds **1**–**13** with carbon numbering.

Thus eqn. (5) is valid for all the molecules studied here, the only exception being C3,5 of **2** which is constant for temperatures over 290 K. In this case we have used only the 223–283 K range for our analysis.

Conformationally mobile compounds

Table 2 presents the carbon chemical shifts of the conformationally mobile molecules studied as a function of temperature in $CDCl_3$. These are: methylcyclohexane (**8**), 2-methylcyclohexanone (**9**), 3-methylcyclohexanone (**10**), 3-methyltetrahydropyran (**11**), 2-methylpiperidine (**12**) and 4-methylpiperidine (**13**).

A common feature of the observed carbon chemical shifts of compounds **8**–**13** as a function of temperature is the absence of any significant curvature. This means that eqn. (4) can only yield two parameters, not the three unknown parameters needed (ΔH, a, c). The true solution can be found provided the difference of the chemical shifts between the conformers is known. Thus from all the possible solutions the one with the expected ($c - a$) value is chosen.

We have observed that for some cases there are two ΔH values for the same difference in chemical shifts ($\Delta\delta$), one easily recognized as the true solution and another very small. This may be understood from the fact that both a high and low value of ΔH may promote the same variation of conformer's mole fraction as a function of temperature.

Methylcyclohexane (8). The coalescence temperature range for this compound was 243–228 K. At 213 K the signals narrow, but they are only from the equatorial conformer. The minor axial conformer was not detected because of the relatively low concentration of our experiments.

Consequently, the curve fitting procedure was applied to 5 points above T_c (at 323, 303, 288, 273 and 258 K). C1, C3,5 and C7 were used for the analysis because they present the largest variations in chemical shift. These shifts in the axial and equatorial conformations are from ref. 9: δC1 27.54 (ax), 33.11 (eq); δC3,5 20.72 (ax), 26.73 (eq); δC7 17.44 (ax), 23.43 (eq). These carbons are shielded by 5.57, 6.01 and 5.99 ppm, respectively, in the axial conformer relative to the equatorial one.

The slope b for the analysis of the methyl carbon and C1 of **8** were provided by C7,8 and C1,4 of **1**, respectively and the slope for C3,5 was taken from **4** (Table 1). The curve fitting procedure

Table 2 ^{13}C chemical shifts of the conformationally mobile compounds at various temperatures in $CDCl_3$ solution

Compd.	Temp./K	C1[a]	C2	C3	C4	C5	C6	C7
8	213	32.64	35.15	26.38	26.02	26.38	35.15	23.29
	228	32.71	35.23	26.44	26.09	26.44	35.23	23.26
	243	32.69	35.25	26.43	26.14	26.43	35.25	23.17
	258	32.69	35.31	26.42	26.21	26.42	35.31	23.08
	273	32.72	35.37	26.44	26.27	26.44	35.37	23.02
	288	32.75	35.43	26.47	26.33	26.47	35.43	22.97
	303	32.78	35.50	26.50	26.39	26.50	35.50	22.91
	323	32.83	35.59	26.53	26.48	26.53	35.59	22.84
9	218	215.73	45.30	36.01	25.10	27.95	42.03	14.77
	228	215.49	45.30	36.04	25.10	27.95	42.02	14.76
	243	215.01	45.32	36.09	25.14	27.97	41.98	14.76
	258	214.64	45.35	36.12	25.17	27.98	41.95	14.75
	273	214.24	45.35	36.14	25.18	27.97	41.91	14.75
	288	213.85	45.38	36.17	25.19	27.97	41.88	14.75
	303	213.49	45.39	36.19	25.20	27.96	41.84	14.75
	318	213.19	45.42	36.21	25.21	27.95	41.82	14.76
	328	213.00	45.43	36.22	25.22	27.95	41.80	14.77
10	223	214.06	49.97	34.25	32.97	25.37	41.15	22.37
	238	213.61	49.97	34.26	33.05	25.37	41.15	22.30
	253	213.26	49.98	34.25	33.11	25.37	41.14	22.25
	268	212.82	49.98	34.24	33.18	25.35	41.14	22.19
	283	212.38	50.00	34.23	33.25	25.33	41.14	22.13
	303	211.88	50.01	34.20	33.33	25.31	41.14	22.06
	313	211.65	50.02	34.19	33.38	25.29	41.14	22.03
	323	211.41	50.04	34.19	33.43	25.29	41.15	22.01
11	213		74.58	31.08	31.70	26.02	68.04	17.69
	228		74.59	31.03	31.74	25.97	68.07	17.63
	243		74.62	31.02	31.76	25.92	68.08	17.58
	258		74.65	31.03	31.83	25.94	68.10	17.56
	273		74.69	31.06	31.90	25.97	68.13	17.53
	288		74.73	31.08	31.98	26.00	68.16	17.49
	303		74.77	31.12	32.06	26.04	68.19	17.47
	323		74.85	31.18	32.16	26.08	68.24	17.44
12	213		51.97	34.08	24.62	25.63	46.84	23.23
	228		52.05	34.21	24.68	25.75	46.92	23.23
	243		52.11	34.34	24.73	25.86	46.98	23.21
	258		52.18	34.47	24.79	25.98	47.05	23.21
	283		52.31	34.68	24.90	26.18	47.18	23.20
	303		52.40	34.86	24.99	26.34	47.27	23.18
	323		52.50	35.03	25.08	26.51	47.36	23.17
13	213		46.60	35.02	31.16	35.02	46.60	22.89
	223		46.65	35.12	31.21	35.12	46.65	22.88
	238		46.69	35.21	31.24	35.21	46.69	22.85
	253		46.71	35.33	31.24	35.33	46.71	22.76
	268		46.77	35.46	31.28	35.46	46.77	22.73
	283		46.83	35.59	31.33	35.59	46.83	22.68
	303		46.91	35.75	31.39	35.75	46.91	22.62
	323		46.95	35.87	31.45	35.87	46.95	22.56

[a] In ppm from TMS.

was carried out for these three carbons and the solutions given were chosen by exactly matching the differences ($c - a$) with the values stated above.

The intercept c of the equatorial conformer found by the curve fitting analysis together with the slope b used from the reference compounds allow the calculation of the chemical shifts of this conformer at 213 K through eqn. (3). These values are: methyl carbon 23.28 ppm (obs. 23.29), C1 32.63 ppm (obs. 32.64), C3,5 26.37 ppm (obs. 26.38 ppm).

2-Methylcyclohexanone (9). The carbons used in the analysis were C6, C7 and C4. The differences in chemical shifts between the two conformers are approximately 3.3 ppm for C6 ($\Delta\delta$C6), 2.3 ppm for C7 ($\Delta\delta$C7) and 5.9 ppm for C4 ($\Delta\delta$C4). These values were taken from *cis*- and *trans*-2-methyl-4-*tert*-butylcyclohexanone (δC6 *cis* 41.34 ppm, *trans* 37.99 ppm, δC4 *cis* 47.11 ppm *trans* 41.23 ppm)[10] and (δC7 *cis* 14.58 ppm, *trans* 16.75 ppm).[11] The slope b was provided by the corresponding carbons of cyclohexanone (**2**). The parameter b for the methyl carbon (C7) was from C7 of **5**.

3-Methylcyclohexanone (10). The carbons used for curve fitting were C3 and C5. The $\Delta\delta$C3 and $\Delta\delta$C5 values were taken from the difference of the chemical shifts of C5 and C3, respectively, of *cis*- and *trans*-2-*tert*-butyl-5-methylcyclohexanone[12] and are 4.0 ppm (δC5 *cis* 32.3 ppm, *trans* 36.3 ppm, δC3 *cis* 24.5 ppm, *trans* 28.5 ppm). (These assignments were made based on the SCS as the original reference did not give any assignments.) The slope for C3 was taken from C3,5 of **7** and for C5 from C3,5 of **2**.

3-Methyltetrahydropyran (11). The only carbon used in the analysis was C5 because there was no other suitable reference compound available for either C3 or the methyl carbon. The slope for C5 was taken from C3,5 of tetrahydropyran (**3**) and the difference in chemical shifts needed for the analysis was calculated by the SCS of methyl[13] at C5 and is 5.2 ppm.

The temperature range used in this case was 323–258 K (5 points). Below 258 K the spectra broadened and even at 213 K, the lowest temperature attainable with $CDCl_3$ as solvent, the peaks were still coalescing. Therefore no comparison could be made between the calculated and observed chemical shift of the equatorial conformer.

Table 3 Calculated intercepts *a* and *c* and conformer energy differences ΔH (kcal mol^{-1}) for the conformationally mobile compounds

Compd.	Atom	*a* (ppm)	*c* (ppm)	*b* (10^4 ppm K^{-1})	$-\Delta H$	$-\Delta H$ (lit.)	$-\Delta H$ MMX	$-\Delta H$ *ab in.*
8	C1	26.16	31.74	41.9	1.91	1.75[a]	1.78	2.15
	C3,5	19.53	25.53	39.3	1.94			
	C7	17.60	23.59	−14.6	1.92			
9	C4	18.40	24.33	42.0	1.60	2.16,[b] 1.33;[e]	2.92	2.38
	C6	39.10	42.25	−6.4	1.58	1.8,[c] 1.57[d]		
	C7	17.30	15.01	−14.9	1.43			
10	C3	29.45	33.97	23.9	1.28	1.1;[c] 1.31;[f]	1.37	1.53
	C5	21.14	25.14	17.7	1.40	1.35,[g] 1.55[h]		
11	C5	19.67	24.87	51.7	1.50	1.44,[i] 1.60[j]	0.99	1.38
12	C4	—	—		>2.6	2.50[k]	2.05	2.60
	C6	—	—		>2.6			
13	C2,6	39.85	45.54	48.7	2.30	1.93[l]	1.74	2.16
	C4	24.81	30.23	41.9	2.35			
	C7	17.22	23.21	−14.6	2.21			

[a] Ref. 16, 17. [b] Ref. 18. [c] Ref. 20. [d] Ref. 19. [e] Ref. 21. [f] Ref. 23. [g] Ref. 22. [h] Ref. 24. [i] Ref. 25. [j] Ref. 26. [k] Ref. 14. [l] Ref. 15.

2-Methylpiperidine (12). The carbons used for the analysis were C4 and C6. The slopes were taken from the corresponding carbons of **6**. No solution could be found. It can only be said that the energy difference between the conformers must exceed 2.6 kcal mol^{-1} in favour of the equatorial conformer based on the chemical shift dependence of **6** and **12**. If the difference in ΔH were 2.60 kcal mol^{-1} the slopes of C4 and C6 of **12** should be smaller than the corresponding slopes of **6** by 0.001 ppm K^{-1} ($\Delta n\Delta\delta/\Delta T$), considering a $\Delta\delta$ value of 6 ppm. The slopes of C4 and C6 of **12** are actually 0.00446 and 0.00475 ppm K^{-1}, respectively while the corresponding slopes of **6** are 0.00439 and 0.00487.

The predominance of the equatorial over the axial conformer can be proved by a simple inspection of the chemical shifts of compounds **12** and **6**.

4-Methylpiperidine (13). The carbons used in the curve fitting were the methyl carbon, C4 and C2. These show the greatest variations in shielding from one conformer to another. The differences in chemical shift for C4 and C2 were calculated using the substituent parameters given by Eliel *et al.*[14] and are approximately 5.5 ppm for both C4 and C2. The difference in chemical shifts of the methyl carbon is 6.00 ppm,[15] very much the same as in **8**.

The slopes *b* for the analysis of the methyl carbon and C4 of **13** were provided by C7,8 and C1,4 of **1**, respectively. The slope for C2 was taken from piperidine (**6**). As in **8** above the chemical shift of the equatorial conformer at 213 K calculated from the *c* and *b* parameters can be compared with the observed values: for the methyl carbon 22.90 ppm (observed 22.89 ppm), for C2 46.58 ppm (observed 46.60) and for C4 31.12 ppm (observed 31.16 ppm).

The greatest source of errors in the above treatment is due to the error of the $\Delta\delta$ values. This error is <±0.20 ppm in **8** and in C7 of **13** because their chemical shifts are known from low temperature measurements. For the other compounds this was considered to be ±0.40 ppm. The error in ΔH due to these uncertainties is ±0.04 kcal mol^{-1} for **8** and C7 of 13 and *ca.* ±0.10 kcal mol^{-1} for the other compounds.

The ^{13}C temperature gradients *b* and the calculated parameters *a*, *c* and ΔH from eqn. (4) for compounds **8**–**13** are given in Table 3. Also given in the table are the conformer energy differences calculated by molecular mechanics (PC Model) and by *ab initio* theory. Density function theory (DFT) was used with the B3LYP/6-31G** basis set in the Gaussian 98 program. Also given are experimental literature values of ΔH.

Discussion

Conformer energy differences

Methylcyclohexane (8). The above analysis using C1, C3,5 and C7 gave a consistent value of the energy difference ΔH (ax–eq) of 1.92 ± 0.05 kcal mol^{-1}. This is slightly greater than the accepted literature value. Direct integration of the methyl carbon signals in a ^{13}C enriched sample[16,17] in $CFCl_3$–$CDCl_3$ (9 : 1) solution at 149–172 K gave ΔH = 1.75 ± 0.05 kcal mol^{-1} and ΔS = −0.03 ± 0.25 cal mol^{-1} K^{-1}.

Interestingly our value is much closer to the calculated *ab initio* value (2.15 kcal mol^{-1}) which of course is for the vapour state (see later). The solvent system used here is much less polar than that used in the low temperature experiments and thus may be closer to the vapour state. It should be noted that the MM calculated value is not for the vapour state. Indeed this energy difference is invariably used to parametrize MM calculations and thus the agreement with the observed value is only to be expected.

2-Methylcyclohexanone (9). The derived values of ΔH from C4 and C6 are in excellent agreement with each other. The value of ΔH from C7 is smaller and should be considered less reliable because of the reduced difference in chemical shifts $\Delta\delta$ (see earlier). Thus our method gives ΔH (ax–eq) = 1.58 ± 0.2 kcal mol^{-1}. This is in complete agreement with the chemical equilibration results of Allinger and Blatter[19] (1.57 kcal mol^{-1}) and also with the less accurate values from LIS techniques in $CDCl_3$ solution[20,21] of ΔG = 1.8 ± 0.3 and ΔG(305 K) = 1.33 kcal mol^{-1} respectively.

This compound has been studied by chemical equilibration methods in propanol[18] by equilibrating 2-methyl-4-*tert*-butylcyclohexanone with an ion exchange resin in the methoxide form which yielded ΔH = 2.16 ± 0.11 kcal mol^{-1} and ΔS = 0.8 ± 0.2 cal mol^{-1} K^{-1} and also in ethanol[19] using sodium ethoxide which resulted in ΔH = 1.57 ± 0.21 kcal mol^{-1} and ΔS = −0.1 ± 0.6 cal mol^{-1} K^{-1}. The latter value is in good agreement with our value. Due to the lower barrier to ring inversion in the cyclohexanone ring, no low temperature studies have been performed for **9**.

The *ab initio* value is considerably higher than both the value found here and that found by the majority of other investigators. We note that the *ab initio* value is for the gas phase and that any C=O···solvent bonding in solution will destabilise the equatorial conformer with respect to the axial form *e.g.* the chloroform–acetone hydrogen bond is *ca.* 5 kcal mol^{-1}[27] and the repulsive steric interaction of the equatorial 2-methyl with the solvent could easily destabilize the equatorial conformer in chloroform solvent by *ca.* 1.0 kcal mol^{-1} as observed.

3-Methylcyclohexanone (10). The derived values of ΔH (ax–eq) from C3 and C5 are in agreement with each other to give ΔH = 1.30 ± 0.1 kcal mol^{-1}. The value of ΔH is in good agreement both with experimental literature values in solution and that calculated by both molecular mechanics and the DFT calculations. Note that the interaction of the solvent with the carbonyl group would not be expected to give rise to any appreciable steric interaction with the 3-methyl group.

LIS techniques[20] in $CDCl_3$ solution gave $\Delta G = 1.1$ kcal mol^{-1} and chemical equilibration in propanol[23] with an ion exchange resin in the methoxide form as base to isomerize 2,5-dimethylcyclohexanone ($\Delta H = 1.31$ kcal mol^{-1}) and 2-*tert*-butyl-5-methylcyclohexanone ($\Delta H = 1.54$ kcal mol^{-1}) and also by heating 2,5-dimethylcyclohexanone at 493 K over Pd/C ($\Delta H = 1.35$ kcal mol^{-1}).[22] The result of the gas phase measurements by resonance-enhanced multiphoton ionization[24] was $\Delta H = 1.55 \pm 0.12$ kcal mol^{-1}.

3-Methyltetrahydropyran (11). The single result shown in Table 3 of $\Delta H = 1.50$ kcal mol^{-1} is in excellent agreement with the published data for this compound. Low temperature NMR in CD_2Cl_2 solution[25] gave ΔG (173 K) $= -1.44 \pm 0.04$ kcal mol^{-1} and resonance-enhanced photon ionization spectroscopy[26] in the gas phase gave $\Delta H = -1.60 \pm 0.10$ kcal mol^{-1}. The observed value of ΔH is also in complete agreement with the calculated *ab initio* value, but the calculated MM value is low.

2-Methylpiperidine (12). The value of the energy difference given from the present experiment is ΔH (ax–eq) > 2.6 kcal mol^{-1} and this is in complete agreement with both the value of Eliel *et al.*[14] of 2.5 kcal mol^{-1} using the counterpoise method and the *ab initio* calculated value. Again the MM value is slightly low.

4-Methylpiperidine (13). The results of the three analyses using C2,6, C4 and C7 are consistent to give $\Delta H = 2.30 \pm 0.10$ kcal mol^{-1}. This value is slightly larger than the value obtained by the low temperature integration method with a ^{13}C enriched sample[15] in $CFCl_3$–$CDCl_3$ (9:1) of 1.93 ± 0.02 kcal mol^{-1}. It is in excellent agreement with the calculated *ab initio* value but again the MM calculated value is lower.

Conclusions

The temperature dependence of ^{13}C chemical shifts can be used to great advantage in conformational analysis. The derived energy differences are consistent when comparing different carbons of the same molecule and agree well with other literature values.

They are somewhat larger than those obtained by the low temperature integration method. This is possibly due to differences in solvation and this is supported by the much better agreement of our values with the *ab initio* (gas phase) calculated values.

We conclude that provided a suitable reference molecule and a good estimate of the differences of chemical shifts of the individual conformers are available, the above method will yield accurate values of the conformer energy differences for potentially any type of solute–solvent pair. Grant and coworkers[28] have shown that the TMS reference used has a small intrinsic temperature dependence, but as Schneider and Freitag have noted previously,[4] this is a constant factor in all the measurements and therefore will not affect the results obtained.

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