Conformational Preferences in Monosubstituted Cyclohexanes Determined by Nuclear Magnetic Resonance Spectroscopy

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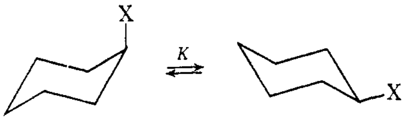
Abstract: *A* values have been obtained for 22 cyclohexane derivatives by the peak area measurement method at about −80° in carbon disulfide utilizing 100-MHz nmr spectrometry. Comparison of several values with those previously reported using this technique indicates that under optimum conditions *A* values accurate to about ±20 cal/mol can routinely be obtained. Results from the various methods employed in obtaining *A* values are compared.

In recent years, considerable effort has been expended in the measurement of conformational preferences in various monosubstituted cyclohexanes. The techniques employed include kinetics,[1,2] chemical equilibration,[3,4] pK_a measurements,[5] electron diffraction,[6] infrared,[7] and nuclear magnetic resonance spectroscopy.[8-10] Presumably, assessment of the conformational preferences of a number of functional groups in monosubstituted cyclohexanes would enable the establishment of a series according to relative steric "sizes." Thus, Winstein and Holness[1] have defined the "*A* value" according to eq 1 and 2. The *A* value, which is expressed in kilocalories/mole, is positive if the equatorial substituent is preferred. In most cases, the axial isomer would be expected to be less stable than the equatorial isomer because of more severe nonbonded interactions.[11]



(1)

$$A = -\Delta F^\circ = RT \ln K \qquad (2)$$

A survey of available compilations of *A*-value data[12] indicates only limited studies have appeared with regard to the effects of solvent,[8,13] concentration, and temperature[14,15] on conformational preferences.

Nuclear magnetic resonance spectroscopy has proven to be extremely valuable in the conformational analysis of monosubstituted cyclohexanes. Although measurement of time-average chemical shifts,[8a-d] line widths,[12b] and coupling constants[8e,16] is of some value in estimating *A* values, the accuracy of these determinations suffers in several respects.

The method utilizing time-average chemical shifts has several inherent difficulties, the most important of which is the problem of locating the positions of the individual axial and equatorial resonances in the absence of rapid exchange. This is usually done by assuming that the chemical shifts of the axial and equatorial resonance of 4-*t*-butylcyclohexyl derivatives are identical with those in the cyclohexyl derivatives in the absence of exchange. Recently,[8f,17] however, work has appeared which clearly demonstrates that these assumptions are invalid and that this method can at best be expected to give values which, except by chance, are only of the right order of magnitude. An alternate chemical-shift method, which extrapolates the chemical shifts obtained at ∼−80° of the methine protons of the monosubstituted cyclohexyl compounds to room temperature by assuming that the effect of temperature upon the positions of these resonances is the same as that of the 4-*t*-butylcyclohexyl derivative, has recently been proposed.[8f] Although this method has not as yet been critically tested, the results appear to be reliable.

As mentioned above, the magnitudes of the time-average coupling constants or the half-widths of the peaks (when the coupling constants are small) have been used to estimate *A* values; however, it is well known that the magnitudes of coupling constants are not absolutely predictable. Furthermore, the accuracy of the determinations is difficult because the coupling constants involved are small. Clearly, this method should be used only when values cannot be obtained by methods known to be reliable.

In the Discussion section, values obtained by the above methods are compared with each other and with values from the peak area method discussed below.

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Whereas values obtained by the peak area measurement are highly reproducible, those obtained by the two methods discussed above clearly are not. In the discussion given below, values which overlap within their reported experimental uncertainties are regarded to be in agreement.

The technique for determining very precise *A* values which unequivocally gives the true conformational preference of the group under consideration is to measure the areas under the axial and equatorial methine proton resonances under conditions of slow ring inversion on the nmr time scale.[9] Unfortunately, the barriers to chair–chair interconversion in monosubstituted cyclohexanes ($\Delta F^{\ddagger} \cong 10$ kcal/mol)[18,19] necessitate spectral determinations at $-80°$ or lower. The measurement of a series of *A* values, albeit at a low temperature, should yield a meaningful series of relative steric bulk, if the determinations are all taken under the same conditions and at the same temperature.

The greater chemical shifts and enhanced sensitivity associated with nmr spectrometers operating at a higher frequency (100 MHz) than previously employed (40 MHz, 60 MHz) make possible the determination of *A* values previously inaccessible at 40 and 60 MHz.

We report here the measurement of 22 *A* values at low temperatures ($\sim -80°$) in essentially the same solvent utilizing the advantages of a 100-MHz nmr spectrometer. Some previously reported values utilizing this technique have been redetermined in order to test its reliability.

Results

The nmr spectra were obtained from a Varian Associates HA-100 nmr spectrometer with a modified cooling system. The temperature was determined using a calibrated copper–constantan thermocouple placed below the sample. Rather serious temperature gradients ($\sim 2°$/in.) were observed in the area of the sample tube rendering enthalpy and entropy calculations meaningless.

The magnitudes of the gradients depend on the gas-flow rate, the spinning rate, tube size, and other factors. To our knowledge, no way of obtaining precise temperature measurements with standard commercially available probes of these types has been reported.

The *A* values were determined by measuring the areas under the axial and equatorial methine proton resonances. Low-, intermediate-, and high-temperature spectra were recorded in order to verify that the resonances observed at low temperature were due indeed to a slowed exchange rate. In all cases, the upfield methine proton resonance was assigned to the axial hydrogen on the basis of the spin–spin splitting pattern[16] and previous data concerning axial *vs.* equatorial chemical shifts in cyclohexyl derivatives.[9,20] The only exception to this trend is the axial methine proton in α-halocyclohexanones which appears downfield from the equatorial methine hydrogen.[21]

For greater sensitivity, the spectrometer was operated in HR mode (field sweep with no internal field-to-frequency lock). Careful selections of sweep rate and radiofrequency power setting were made in order to ensure that differential saturation effects were negligible compared to other sources of experimental error (Table I). The observation that *K* appears to decrease as the power is increased is to be expected on the basis of the following argument. The interconversion of the two species allows an additional mechanism for relaxation even if it is assumed that the relaxation of each resonance is the same in the absence of conformational isomerization. In cases where a definite conformational preference exists, the half-life of a molecule in the less stable conformation is less than that of a molecule in the more stable form. At $-80°$ the conformers still interconvert several times a second. By the process of interconversion the molecules of the less stable conformer are replaced by unsaturated molecules faster than those of the more stable isomer; therefore, the peaks which correspond to the less stable conformer should tend to saturate less readily than those of the more stable form causing the apparent equilibrium constant to decrease as the power is increased.

Table I. The Effect of Varying Radiofrequency Power on the Observed Equilibrium Constant for Iodocyclohexane at Constant Field-Sweep Rate

Radiofrequency attenuation, db	K^a = [eq]/[ax]
54	2.96 ± 0.06
57	3.10 ± 0.05
63	3.30 ± 0.05
70	3.39 ± 0.10
75	3.29 ± 0.29

[a] The value of *K* is the average of four to ten separate determinations. The uncertainty reported is the maximum observed deviation in *K*.

Each *A* value was calculated from data obtained from at least ten scans at one temperature, and the relative areas under the axial and equatorial peaks were determined by hand planimetry. Spectral calibrations were effected in the usual manner in frequency-sweep mode.

The generally used solvent system consisted of tetramethylsilane–carbon disulfide, 10:90 by volume, with the concentration of monosubstituted cyclohexane at 2.2 ± 0.2 *M*. Cyclohexyl mercaptan was studied at two concentrations (1.1 and 2.2 *M*). Cyclohexyl *p*-toluenesulfonate (1.0 *M*) and cyclohexyl methanesulfonate (1.0 *M*) were examined in carbon disulfide–deuteriochloroform–tetramethylsilane, 40:50:10 by volume. Cyclohexyl mercuric acetate (0.5 *M*) was observed in carbon disulfide–pyridine–tetramethylsilane, 70:20:10 by volume. The pertinent data are collected in Table II.

A few of the spectra exhibited troublesome behavior. In fluorocyclohexane, the geminal hydrogen–fluorine coupling constant (J_{HF}) is 48 Hz while the chemical-shift difference between axial and equatorial methine proton resonances ($\Delta\nu_{\mathrm{ae}}$) is 44 Hz. As a result, the axial proton resonance of the H–C–F downfield doublet[19] ($J_{\mathrm{HF}} = 48$ Hz) overlaps with the equatorial proton resonance of the H–C–F upfield doublet under condi-

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Table II. *A* Values at 100 MHz[a]

Substituent	Concn, *M*	ν_{ax},[a,b] Hz	ν_{e},[a,b] Hz	$\Delta\nu$, Hz	Temp,[c] °C	K[d]	ΔF[d,e]	Prior ref
H ($C_6D_{11}H$)	2.50			51	−80	1.04 ± 0.04	0.015 ± 0.015	*j*
HgOAc	0.38[f]	234	298	64	−79	1.00 ± 0.20	0.00 ± 0.09	*k*
$N{\rightleftarrows}C$	2.02	333	384	51	−80	1.73 ± 0.04	0.210 ± 0.013	None
$C{\equiv}N$	2.05	240	292	52	−79	1.88 ± 0.11	0.24 ± 0.003	*l, m*
F	2.11	421	465	44	−86	2.10 ± 0.05	0.276 ± 0.015	6, 8c, 9, 26, *n*
$N{=}C{=}S$	2.01	352	403	51	−79	2.09 ± 0.04	0.284 ± 0.013	None
$C{\equiv}CH$	2.04	209	271	62	−80	2.90 ± 0.30[h]	0.41 ± 0.05	*o*
I	1.98	406	479	78	−80	3.39 ± 0.10	0.468 ± 0.021	9, 10
Br	2.15	390	460	70	−81	3.48 ± 0.03	0.476 ± 0.013	7, 8c–f, 9, 10, 15, *p*
$N{=}C{=}O$	1.96	318	380	62	−80	3.74 ± 0.09	0.506 ± 0.020	*q*
OTs	1.00[g]	419	462	43	−80	3.83 ± 0.10	0.515 ± 0.021	1, 14, *r, s*
Cl	2.01	370	440	70	−81	3.99 ± 0.08	0.528 ± 0.019	8c,d,f, 9, 10, 15, 17, *t–v*
OCD_3	2.13	292	334	42	−82	4.23 ± 0.08	0.547 ± 0.019	3, *r*
OSO_2CH_3	1.00[g]	452	496	44	−88	4.63 ± 0.20	0.56 ± 0.03	None
$OC({=}O)H$	2.04	461	500	39	−80	4.62 ± 0.22	0.59 ± 0.03	*w*
$SiCl_3$	2.13	405	457	52	−80	4.92 ± 0.30	0.61 ± 0.04	None
OAc	2.01	444	482	38	−88	6.95 ± 0.60	0.71 ± 0.05	8f,13,14, *r, w, x*
NO_2	1.77	425	444	19	−90	18.0 ± 5.00[i]	1.05 ± 0.14	4, 10, 12b, 16, *q, y*
SCD_3	2.02	236	293	57	−79	16.1 ± 0.60	1.07 ± 0.04	*z*
SH	1.07	257	341	84	−80	21.3 ± 0.90	1.17 ± 0.04	*z, aa*
SH	2.18	257	341	84	−80	23. ± 0.60	1.20 ± 0.04	
$SC{\equiv}N$	2.08	307	402	95	−79	24.3 ± 1.60	1.23 ± 0.05	None
$C({=}O)OCH_3$	2.00	214	253	39	−78	29.0 ± 5.00	1.31 ± 0.10	*bb–dd*

[a] Except where indicated the solvent is CS_2–TMS 90:10, by volume. [b] Measured from TMS (internal standard). [c] Maximum uncertainty in $T = \pm 4°$. [d] The uncertainty reported is the maximum observed deviation. [e] The uncertainty reported is the sum of the effects of the maximum uncertainty in *K* and *T*. [f] Solvent = pyridine–TMS–CS_2, 25:75:67.5 by volume. [g] Solvent = TMS–CS_2–$CDCl_3$, 4:43:53 by volume. [h] Axial proton signal not separated from remaining ring protons. *A* value determined by comparing the area of the equatorial proton signal to that of the remaining protons. [i] Axial and equatorial resonances are separated by only 20 Hz and spin-coupled resonances overlap. *A* value measured and decoupled spectra obtained in HA-operational mode. [j] R. A. Bovey, F. P. Hood, III, E. W. Anderson, and R. L. Kornegay, *J. Chem. Phys.*, **41**, 2041 (1964). [k] F. R. Jensen and L. H. Gale, *J. Am. Chem. Soc.*, **81**, 6337 (1959). [l] N. L. Allinger and W. Szkrybalo, *J. Org. Chem.*, **27**, 4601 (1962). [m] B. Rickborn and F. R. Jensen, *ibid.*, **27**, 4606 (1962). [n] F. P. Hood and R. L. Kornegay, *J. Chem. Phys.*, **40**, 3099 (1964). [o] R. J. Ouellette, *J. Am. Chem. Soc.*, **86**, 3089 (1964). [p] E. L. Eliel and R. G. Haber, *ibid.*, **81**, 1249 (1959). [q] G. C. Corfield and A. Crawshaw, *Chem. Commun.*, 1044 (1967). [r] E. L. Eliel and M. H. Gianni, *Tetrahedron Letters*, 97 (1962). [s] E. L. Eliel and R. S. Ro, *Chem. Ind.* (London), 251 (1956); E. L. Eliel and R. S. Ro, *J. Am. Chem. Soc.*, **79**, 5995 (1957). [t] V. A. Atkinson, *Acta Chem. Scand.*, **15**, 599 (1961). [u] K. Kozima and K. Sakashita, *Bull. Chem. Soc. Japan*, **31**, 796 (1958). [v] N. L. Allinger and C. D. Liang, *J. Org. Chem.*, **32**, 2391 (1967). [w] E. A. Allen, E. Premuzic, and L. W. Reeves, *Can. J. Chem.*, **41**, 204 (1963). [x] N. B. Chapman, R. E. Parker, and P. J. A. Smith, *J. Chem. Soc.*, 3634 (1960). [y] H. Feltkamp and N. C. Franklin, *J. Am. Chem. Soc.*, **87**, 1616 (1965). [z] E. L. Eliel and B. P. Thill, *Chem. Ind.* (London), 88 (1963). [aa] G. Chiurdoglu, J. Reisse, and M. Van der Stichelen Rogier, *ibid.*, 1874 (1961). [bb] N. L. Allinger and R. J. Curby, *J. Org. Chem.*, **26**, 933 (1961). [cc] E. A. S. Cavell, N. B. Chapman, and M. D. Johnson, *J. Chem. Soc.*, 1413 (1960). [dd] M. Tichy, J. Jonas, and J. Sicher, *Collection Czech. Chem. Commun.*, **24**, 3434 (1959).

tions of slow exchange on the nmr time scale (Figure 1a). Consequently, the equilibrium constant was obtained by measuring the areas under the two outside peaks. This did not, however, appreciably affect the accuracy of the determination.

Rather severe overlap of the axial proton resonance with the methylene protons resonance occurred in the case of cyclohexylacetylene and carbomethoxycyclohexane at low temperature. In the case of carbomethoxycyclohexane, it was possible to estimate the area under the axial proton resonance by subtracting the overlap due to the methylene proton resonance. In cyclohexylacetylene, the axial proton resonance essentially disappeared under the methylene protons resonance; consequently, the technique in this case was to compare the area under the well-separated equatorial methine proton signal to the area under all other resonances. The area ratio of the time-average methine proton signal to all other resonances was also measured at high temperature and any needed correction applied at −80°.

The nmr spectrum of the methine protons of equatorial and axial cyclohexylmercuric acetate at −80° was complicated by the presence of ^{199}Hg sidebands and/or impurities under the axial proton peak. The estimated error is reported in Table II.

Upon examination of the H–C–NO_2 resonance of nitrocyclohexane at −90°, the presence of two resonances was not discernible; however, upon irradiation near the β-protons resonance, the spectrum simplified considerably revealing two resonances separated by 20 Hz (Figure 1b). Upon warming, the two resonances coalesced in the usual manner. The observed chemical-shift difference between axial and equatorial proton resonances in nitrocyclohexane ($\Delta\nu_{ae}$ 20 Hz) is in agreement with that between the H–C–NO_2 resonances in *cis*- and *trans*-4-*t*-butylnitrocyclohexane ($\Delta\nu_{ae}$ 20 Hz).[22]

The analysis of the spectra of the remaining monosubstituted cyclohexanes was straightforward as exemplified by the axial and equatorial H–C–I resonances of iodocyclohexane (Figure 1c) at −80°.

Discussion

In Table III the *A* values for the cyclohexyl halides obtained by the low-temperature peak area measurement method are compiled. Also listed are the values (report VII) obtained by a time-average resonance position method which will be discussed below. The values will be considered collectively first, and then later in the paper individual determinations will be discussed.

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Table III. *A* Values for Cyclohexyl Halides Obtained by Low-Temperature Nmr Measurements in Carbon Disulfide Solution

			A values, kcal/mol			
Report	Method	Temp, °C	$C_6H_{11}F$	$C_6H_{11}Cl$	$C_6H_{11}Br$	$C_6H_{11}I$
I	60 MHz, area ratios[a]	−81	0.250	0.513	0.480	0.431
II	*b*	∼−73		0.510	0.474	0.454
III	100 MHz, area ratios[c]	−80	0.276[g]	0.528	0.476	0.468
			±0.015	±0.019	±0.013	±0.021
IV	100 MHz, area ratios	−83		0.53	0.49	
V	40 MHz, area ratios[d]	−100		0.406	0.511	
VI	60 MHz, area ratios[e]	−55	0.242			
VII	60 MHz, extrapolation of time-average signal to low temperature[f]	−81	0.241[h]	0.478	0.439	0.407

[a] Reference 9. [b] These *A* values were calculated from the per cent conformer populations reported in ref 10 assuming a measurement temperature of −75.0°. [c] This study. [d] Reference 18. [e] Reference 19. [f] Reference 9. [g] Temperature −86°. [h] Temperature −93°. [i] 0.5 *M* in CS_2 containing 15% TMS by volume, ref 8f.

The very close agreement of the values in reports I, II, III, IV, and VI attest to the high accuracy obtainable by the area measurement method. Also, it should be emphasized that these values result from a direct measurement of the concentration of the conformers, not from secondary criteria such as rates of substitution data which might be influenced by other effects. *No approximations* are made in obtaining these data and *no assumptions* whatsoever are necessary in carrying out the calculations. Clearly, whenever the experiments are carefully and properly carried out, this method at the present time represents the ultimate in obtaining precise *A* values. A disadvantage is that values can be obtained only at low temperature using this method. However, in a recent study,[8f,17] values of ΔS for the equatorial–axial conversions in carbon disulfide solution for bromo, chloro, trifluoroacetate, cyano, and acetate have been estimated to be less than 1 eu. Thus, it appears that *A* values obtained in nonpolar solvents at −80° are expected to be within 0.1 kcal/mol of room-temperature values.

The values in report V of Table III were taken at 40 MHz. Although these values are closer to those in reports I–IV than usually obtained by other methods, they clearly are not in accord with the agreement between reports I–IV. At 40 MHz the resonances are not sufficiently separated to give meaningful values. This is clear upon inspection of the published spectra taken at 40 MHz.[18]

The conformational preferences in report VII of Table III[9] were obtained by measuring the position of the time-average signal at room temperature and several intermediate lower temperatures (under conditions of fast exchange) and then, by direct extrapolation, values for the time-average resonances at −81° (−93° for $C_6H_{11}F$) were obtained.[23] *A* values were then calculated using these extrapolated time-average values and the measured axial and equatorial resonances. Although this method is to be expected to give considerably better values than those obtained by utilizing time-average resonances in conjunction with axial and equatorial resonances in locked compounds, the results show considerable variation from those obtained by the more accurate peak area measurement method.

When *A* values obtained by peak area measurements are compared with those obtained by other procedures utilizing nmr techniques, significant variations are generally observed. Many such examples are given below. Differences in solvent and temperature may in part be responsible for the apparent discrepancies, but the principal sources of the variations very likely lie in the invalidity of the assumptions made in measurements obtained by methods other than peak area determinations.

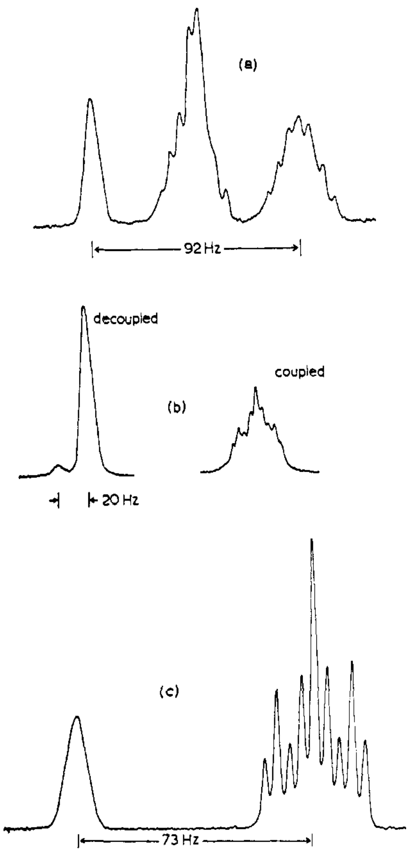

Figure 1. Spectra (100 MHz) at low temperature of H–C–X resonances of monosubstituted cyclohexanes: (a) ⌬-F at −86°, (b) ⌬-NO_2 at −90°, (c) ⌬-I at −80°.

For example, consider the *A* value for the bromo group. At low temperature (−80°) the unequivocal

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(23) This work has been misquoted as being extrapolated to room temperature.[8c,12a,c]

value, in carbon disulfide by peak area measurements, is 0.48 kcal/mol. Upon observing a parallelism between the temperature dependence of the chemical shifts of the axial and equatorial CHBr proton resonances in cyclohexyl bromide and the *cis*- and *trans*-4-*t*-butylcyclohexyl bromides at low temperatures, it was proposed that the axial and equatorial proton resonances which would be observed in the absence of exchange for cyclohexyl bromide at room temperature necessary for calculation of the corresponding *A* value might be obtained by the appropriate extrapolations. Utilizing this procedure an *A* value for bromine of 0.55 kcal/mol at 25° is obtained.[8f] Several determinations of the bromo *A* value have been reported at about room temperature using techniques not involving nmr spectroscopy. The *A* values obtained are all larger than 0.48 kcal/mol except for an estimate of 0.26 kcal/mol obtained by Kerr constant measurements. A kinetic study involving the measurement of the rates of bimolecular substitution and elimination of cyclohexyl bromide and *cis*- and *trans*-4-*t*-butylcyclohexyl bromide with thiophenolate in 87% ethanol gave an *A* value of 0.73 kcal/mol at 25°.[24,25] Utilizing infrared spectroscopy, including corrections for unequal axial and equatorial extinction coefficients, a value of 0.61 kcal/mol at 30° was reported.[7] Booth[8e] obtained an *A* value for the bromo substituent at room temperature of 0.7 ± 0.2 kcal/mol by the coupling-constant nmr method.

At about room temperature by comparing the time-average resonance of the methine proton in cyclohexyl bromide with the corresponding axial and equatorial resonances of the 4-*t*-butylcyclohexyl bromides, Eliel and coworkers have reported *A* values for the bromo group of about 0.36 kcal/mol[8c] in CS_2. This method requires the assumption that the chemical shift of the axial and equatorial proton of the cyclohexyl derivative is identical with that in the corresponding 4-*t*-butyl derivatives, but the bulk of the available data indicates that this assumption is incorrect.[8b,f] As cited above, most of the available data indicate that at room temperature the *A* value for bromo is larger than 0.5 kcal/mol.

Reisse, Celotti, and Chiurdoglu[8d] have reported a study of the temperature dependence of the equilibrium constant for bromocyclohexane obtained by a slight modification of the method used by Eliel and coworkers. The values they obtained for bromocyclohexane at room temperature are near those obtained by Eliel. Using the values of ΔH and ΔS measured by Reiss and coworkers a value for ΔF at −80° of 0.350 ± 0.020 kcal/mol can be calculated, whereas the correct value is 0.48 kcal/mol (Table II).

Conformational favoritism in the other halocyclohexanes has also been studied to a great extent. All previous results indicate that fluorine has the lowest *A* value of all the halogens. An electron diffraction analysis of fluorocyclohexane[6] gave an estimate (uncertainty reported unobtainable) of the energy difference of 0.17 kcal/mol at room temperature (?) between equatorial and axial fluorine with equatorial fluorine favored. Two studies at low temperature of the proton[9] and fluorine[26] magnetic resonance spectra of fluorocyclohexane gave *A* values of 0.25 kcal/mol (−93° in CS_2)[9] and 0.24 kcal/mol (−55° in $CFCl_3$).[26] The small discrepancy between the value reported here (A = 0.28 kcal/mol at −86° in CS_2) and previous values[9,26] could be attributed to concentration differences,[9] to solvent,[26] and to the possibility of differential saturation effects in the previous studies. Values estimated by the chemical shift method appear lower, ~0.15 kcal/mol.[8c]

An electron-diffraction analysis of chlorocyclohexane[27] indicated that it existed as 45 ± 5% axial chlorocyclohexane giving an energy difference of less than 0.3 kcal/mol between the two conformations. A number of studies utilizing infrared spectroscopy have been carried out on chlorocyclohexane. Kozima and Sakashita[28] observed that equatorial chlorocyclohexane is more stable than the axial isomer ($\Delta H_{\text{eq-ax}} = 0.33$ kcal/mol in CS_2, 0.34 kcal/mol in the vapor phase, 0.44 kcal/mol in methyl acetate). Allinger and Liang[29] utilizing ir spectroscopy reported an *A* value for chlorine of 0.4 kcal/mol at room temperature. Chiurdoglu and coworkers[15] obtained ir data from which an *A* value of 0.72 kcal/mol at 26° in CS_2 was calculated. Low-temperature nmr studies involving the direct measurement of conformational concentrations have been reported to give *A* values of 0.51 kcal/mol[10] at −75° in CS_2, 0.51 kcal/mol in CS_2 at −81°,[9] and 0.41 kcal/mol[18] at −80° in CS_2; however, the accuracy of the latter value suffers somewhat due to a low operating frequency (40 MHz) and a high signal to noise ratio. By extrapolating the chemical shifts of the methine protons in cyclohexyl chloride to room temperature, assuming their variation with temperature is the same as that in the 4-*t*-butylcyclohexyl derivatives, a value of 0.56 was obtained.[8f] Estimates by the chemical shift method of Eliel and coworkers are lower, 0.42 kcal/mol.[8c,d]

Previous studies have indicated that although iodine has the largest van der Waals radius of all the halogens, it has a remarkable low *A* value. From low-temperature nmr studies, *A* values for iodide were assigned as 0.43 kcal/mol at −81° in CS_2[9] and 0.43 kcal/mol at −75° in CS_2.[10] These values are in agreement with that reported here (A = 0.47 kcal/mol at −80° in CS_2).

The observed steric bulk sequence (Table II) for the halogens ($F < I < Br < Cl$) has been explained previously.[9] The observation that fluorine is the "smallest" halogen is not surprising in light of its van der Waals radius; however, the remainder of the sequence obviously does not parallel van der Waals radii. The trend can be rationalized on the basis of bond lengths (Table IV) and polarizabilities. The longer the carbon–halogen bond and the more polarizable the electron cloud surrounding the halogen atom, the more diminished are the nonbonded compressions in the axial isomer and the lower the *A* value.

The substituents studied are compiled in order of increasing *A* values in Table II. It is apparent that van der Waals radii, bond lengths, polarizabilities, and cylindrical symmetry all play important roles in determining the observed sequence. Consideration

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(24) See Table II, footnote *p*.

(25) E. L. Eliel and R. G. Haber, *Chem. Ind.* (London), 264 (1958).

(26) See Table II, footnote *n*.

(27) See Table II, footnote *t*.

(28) See Table II, footnote *u*.

(29) See Table II, footnote *v*.

Table IV. Carbon–Halogen Bond Lengths[a]

Halogen	Bond length, Å	Halogen	Bond length, Å
F	1.49	Br	1.91
Cl	1.76	I	2.00

[a] G. W. Wheland, "Resonance in Organic Chemistry," John Wiley & Sons, Inc., New York, N. Y., 1955, pp 701, 713.

of Table II reveals some interesting trends and "anomalies."

The van der Waals radii of sulfur (1.85 Å) and oxygen (1.40 Å)[30] seem to play important roles in determining the conformational preference of substituents with oxygen or sulfur bound to the cyclohexane ring. The *A* values in the oxygen series lie in a narrow range (0.5–0.7 kcal/mol), while the sulfur analogs occur in a comparable narrow range (1.1–1.2 kcal/mol), but are of substantially greater magnitude. A meaningful comparison can be made between the -OCD$_3$ group ($A = 0.55$ kcal/mol at $-82°$ in CS$_2$) and the -SCD$_3$ group ($A = 1.07$ kcal/mol at $-79°$ in CS$_2$).

The *A* value obtained at $-82°$ for the -OCD$_3$ group is 0.55 kcal/mol (Table II). Previous values for -OCH$_3$ are 0.74 kcal/mol in water at 100° (obtained from a study of the equilibrium between *cis*-4-methoxy-*cis*-3-hydroxycyclohexanecarboxylic acid and its lactone), and 0.6 kcal/mol at ambient probe temperature (*ca.* 37°) in CCl$_4$ (measured by the chemical-shift method of Eliel[31]). The observation of two resonances at low temperature corresponding to the axial and equatorial methine protons of trideuteriomethoxycyclohexane is in contradiction to the suggestion of Reeves and Strømme[32] that the rate of ring inversion in methoxycyclohexane may still be rapid on the nmr time scale at $-110°$. This report probably arose in part from nonrecognition that the methine and methyl resonances occur at almost identical chemical shifts.

It is interesting to note the difference between the *A* value for the *p*-toluenesulfonate group ($A = 0.52$ kcal/mol at $-80°$ in CS$_2$–CDCl$_3$) and the methanesulfonate group ($A = 0.56$ kcal/mol at $-88°$ in CS$_2$–CDCl$_3$) reported in Table II. Assuming *A* values are a reliable measure of conformational preferences, the simplest explanation for the observed order is that the *p*-methylphenyl group can assume a conformation or conformations in axial cyclohexyl *p*-toluenesulfonate which have a reduced relative steric bulk compared to a methyl group in methanesulfonate.

The *A* value of the *p*-toluenesulfonate functionality obtained from a comparison of the solvolysis rates of cyclohexyl *p*-toluenesulfonate and *cis*- and *trans*-4-*t*-butylcyclohexyl *p*-toluenesulfonates ($A = 1.7$ kcal/mol at 50° in ethanol–acetic acid–formic acid)[1] is at strong variance with the value reported here. However, another kinetic study involving the reaction of the appropriate *p*-toluenesulfonates with sodium thiophenolate in 90% aqueous ethanol at 25° gave an *A* value for *p*-toluenesulfonate ($A = 0.7$ kcal/mol)[33] more in line with the value reported here. Using the chemical shift method of Eliel,[8] Celotti and coworkers[14] obtained an *A* value for *p*-toluenesulfonate of 0.209 kcal/mol at 36° in CCl$_4$; however, using the same experimental technique, Eliel and Gianni obtained an *A* value for *p*-toluenesulfonate of 0.6 kcal/mol at 37° in CCl$_4$. (The values reported here were obtained in cooperation with Professor Noyce and his coworkers. Interpretation of reasons for the difference for the tosylate obtained by the nmr method and by solvolysis of 4-*t*-butylcyclohexyl tosylates[1] will be presented elsewhere by them.)

Few reports have appeared concerning the conformational preference of the formyl group on the cyclohexane ring. By comparing the position of the time-average H–C–O proton resonance with the shifts of axial and equatorial methine proton resonances in 2,2,6,6-tetradeuteriocyclohexyl formate at low temperature, one group of workers[34] obtained an *A* value for formate of 0.24 kcal/mol at 25°. The accuracy of this determination suffers from the small chemical-shift difference (14.9 Hz) between axial and equatorial proton resonances at the operating frequency (40 MHz) used. The above result disagrees considerably with the *A* value (0.59 kcal/mol at $-80°$ in CS$_2$) reported in Table II.

There has been considerable effort expended toward the measurement of the *A* value of the acetoxyl group, but no reports have appeared employing the technique used in this study, *i.e.*, peak area measurements of nmr spectra at low temperature. A kinetic study of the alkaline hydrolysis of *cis*- and *trans*-4-*t*-butylcyclohexyl acetate and cyclohexyl acetate in 1:1 water–dioxane gave an *A* value for acetoxyl of 1.5 kcal/mol[35] at 40°. This value is at variance with the value reported here ($A = 0.71$ kcal/mol at $-88°$ in CS$_2$). Using the chemical shift method, Celotti and coworkers[14] obtained an *A* value of 0.407 kcal/mol (37°, CCl$_4$) and Eliel and Gianni[31] a value of 0.7 kcal/mol (37°, CCl$_4$). From the data of Allen, Premuzic, and Reeves[34] an *A* value of 0.66 kcal/mol (25°, CS$_2$) can be calculated. Using a coupling constant analysis, Anet[13] obtained an *A* value for acetoxyl of 0.66 kcal/mol (28°, CS$_2$). By extrapolating the low-temperature chemical shifts to 25° assuming the temperature dependence of the resonance of the methine protons in the cyclohexyl derivative is the same as that in the corresponding 4-*t*-butylcyclohexyl derivatives, an *A* value of 0.63 kcal/mol has been calculated.[8f]

It is apparent from Table II and previous results[34] that the formate group is observed to have a consistently smaller *A* value than acetate. Although the overriding factor in determining the conformational requirements of acetate and formate is the oxygen atom bound to the ring, the methyl group of acetate appears to exert a significant steric effect.

Assessment of the conformational preference of sulfur bound to the cyclohexane ring has received little attention. A variable-temperature infrared spectroscopic study of cyclohexanethiol led Chiurdoglu and coworkers[36] to conclude that the axial isomer is favored over the equatorial isomer ($\Delta H_{\text{eq-ax}} = +0.41 \pm 0.04$ kcal/mol). This result would require a prohibitively

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[30] L. Pauling, "The Nature of the Chemical Bond," 3rd ed, Cornell University Press, Ithaca, N. Y., 1960, p 260.

[31] See Table II, footnote *r*.

[32] L. W. Reeves and K. O. Strømme, *Trans. Faraday Soc.*, **57**, 390 (1961).

[33] See Table II, footnote *s*.

[34] See Table II, footnote *w*.

[35] See Table II, footnote *x*.

[36] See Table II, footnote *aa*.

high contribution of entropy ($\Delta S_{eq-ax} = +8$ eu) to account for the result reported here ($A = 1.2$ kcal/mol at $-80°$ in CS_2) and may be due to incorrect peak assignments in the infrared spectrum. Using the position of the time-average methine proton resonance of cyclohexanethiol, Eliel and Thill obtained an estimate of the A value for sulfhydryl of 0.9 kcal/mol (25°, CCl_4).[37] It is interesting to note in Table II that cyclohexanethiol gave essentially the same A value for sulfhydryl at substantially different concentrations. This would suggest no appreciable association in this concentration range.

The A values of the $-SC_6H_5$[31] and $-SCH_3$[37] groups have been reported to be 0.8 kcal/mol and about 0.7 kcal/mol, respectively, in CCl_4 at room temperature. The latter value agrees in magnitude only with the A value of the $-SCD_3$ group reported here ($A = 1.07$ kcal/mol at $-79°$ in CS_2).

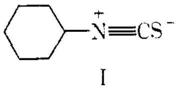
No reports have appeared concerning the conformational preference of the thiocyanate group on a cyclohexane ring. The large preference of the $-SCN$ functionality for the equatorial position ($A = 1.2$ kcal/mol at $-79°$ in CS_2) is not unexpected in light of the results for other sulfur-containing groups; however, the smaller A value observed for $-SCD_3$ ($A = 1.07$ kcal/mol at $-79°$ in CS_2) is interesting in view of methyl being much more sterically bulky than cyano.

Functionalities which can be considered to be cylindrically symmetrical are found to have relatively low conformational preferences. Thus, the A values reported here of nitrile ($A = 0.24$ kcal/mol at $-79°$ in CS_2), isonitrile (0.21 kcal/mol at $-80°$ in CS_2), and ethynyl (0.41 kcal/mol at $-80°$ in CS_2) groups are relatively small. Previous workers have also observed a small A value for the cyano group in tetrahydrofuran as solvent ($A = 0.25$ kcal/mol at 66°)[38] 0.23 kcal/mol (25° in CS_2),[8f] and in *t*-butyl alcohol ($A = 0.15$ kcal/mol at 25°).[39] In the latter study[39] it was observed that the conformational preference was due predominantly to a position entropy term ($\Delta S_{eq-ax} = +0.7$ eu $\pm$ 0.3 eu; $\Delta H_{eq-ax} = +0.04 \pm 0.1$ kcal/mol).

There have been no previous reports of the A value of the isocyano group; however, the A value of 0.24 kcal/mol at $-80°$ reported here is not unexpected. The slightly smaller A value for the isocyano functionality can be rationalized on the basis of the formal positive charge on nitrogen reducing the electron density about nitrogen.

The steric requirements of the ethynyl group have been estimated indirectly by an nmr study of the position of the hydroxyl proton resonance of 1-ethynylcyclohexanol at various concentrations in carbon tetrachloride.[40] The observed A value (0.18 kcal/mol at 41°) is certainly consistent with the ethynyl functionality being "small," but the result is in qualitative agreement only with that reported here ($A = 0.41$ kcal/mol at $-80°$ in CS_2). It is interesting to note the vastly reduced A value of the ethynyl group as compared to the vinyl substituent ($A = 1.39$ kcal/mol in CCl_4 at 38°).[41]

The A values of the isocyanate ($A = 0.51$ kcal/mol at $-80°$ in CS_2) and isothiocyanate ($A = 0.28$ kcal/mol at $-79°$ in CS_2) functionalities reported here again illustrate the reduced conformational requirements of linear, cylindrical groups; however, one might predict on the basis of van der Waals radii that if either group should be larger, isothiocyanate would be larger than isocyanate. The obvious inconsistency of the results with such a prediction might suggest that canonical structures such as I are more important in cyclohexyl isothiocyanate than in the analogous isocyanate. Previous investigators[42] found the value in deuteriochloroform at 35° to be 0.39 kcal/mol and 0.48 kcal/mol by chemical-shift and band-width methods, respectively. These values again illustrate the large uncertainty in these methods.



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Investigations toward the measurement of the A value of the nitro group have indicated that it is indeed a large functionality. Two nmr studies utilizing the time-average values of the $H-C-NO_2$ chemical shift[10] and spin-spin splitting pattern[16] incorrectly concluded that nitrocyclohexane existed *exclusively* as the equatorial isomer at room temperature. A study of the equilibration of *cis*- and *trans*-4-*t*-butylnitrocyclohexane by potassium *t*-butoxide in *t*-butyl alcohol[4] gave thermodynamic parameters ($\Delta H_{eq-ax} = -0.98$ kcal/mol, $\Delta S_{eq-ax} = +0.6$ eu, or $A = 1.1$ kcal/mol at $-90°$) in good agreement with the value reported here ($A = 1.05$ kcal/mol at $-90°$ in CS_2) as is the value of 1.02 kcal/mol obtained by Feltkamp and Franklin.[43]

Many previous workers have observed that the A value of the carbomethoxy group is large. A study of the epimerization of the dimethyl esters of 5-*t*-butylcyclohexane-1,3-dicarboxylic acid in aqueous methanol gave an A value of 1.05 kcal/mol at 25° for the carbomethoxy group.[44] A similar study concerning the equilibration of *cis*- and *trans*-1,3-dicarbomethoxycyclohexane using sodium methoxide in methanol indicated a large preference of carbomethoxy for the equatorial position ($\Delta H = -1.05$ kcal/mol).[45] Another group was able to infer from the rates of alkaline hydrolysis in aqueous dioxane of the appropriate cyclohexane carboxylate esters that the A value of the carbomethoxy group is quite large.[46] The previously reported values are in good agreement with that reported here ($A = 1.3$ kcal/mol at $-78°$ in CS_2). The somewhat smaller A value of carbomethoxy compared to methyl ($A \cong 1.8$ kcal/mol) is not unexpected due to the ability of the planar carbomethoxy group to assume a conformation in the axial position so as to minimize nonbonded interactions. The somewhat higher A value for carboxyl (1.6–1.7 kcal/mol)[5,47] is due presumably to preferential association of the equatorial isomer.

The effect of long bond length and polarizability is again reflected in the observed A values of the trichloro-

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[37] See Table II, footnote *z*.

[38] See Table II, footnote *l*.

[39] See Table II, footnote *m*.

[40] See Table II, footnote *o*.

[41] R. J. Ouellette, K. Liptak, and G. E. Booth, *J. Org. Chem.*, **31**, 546 (1966).

[42] See Table II, footnote *q*.

[43] See Table II, footnote *y*.

[44] B. J. Armitage, G. W. Kenner, and M. J. T. Robinson, *Tetrahedron*, **20**, 747 (1964).

[45] See Table II, footnote *bb*.

[46] See Table II, footnote *cc*.

[47] See Table II, footnote *dd*.

silyl group (A = 0.61 kcal/mol at −80° in CS_2) and acetatomercuri group (A = 0.010 kcal/mol at −79° in CS_2-pyridine). The group radius of the -$SiCl_3$ functionality is almost certainly larger than methyl, but the longer carbon–silicon bond negates the effect of a large, bulky substituent. There have been no previous reports concerning the A value of -$SiCl_3$. The A value of the bromomercuri group has been observed to be essentially zero in pyridine at 95°.[48]

As has been previously reported,[49] the conformational preference of hydrogen in cyclohexane-d_{11} is very small or zero.

Experimental Section

Nmr Methods. The spectra were obtained on a Varian HA-100 nmr spectrometer in which the sensor was replaced by a thermocouple. The temperature of the coolant gas was regulated by a split-stream technique which allowed precise control and excellent temperature stability. The precautions taken to ensure that the accuracy of the equilibrium constants was not affected by saturation are discussed above as is the calibration of the temperature and measurement of the relative areas. Each spectrum was carefully examined under conditions of very rapid exchange, slow exchange, and throughout the region of the intermediate exchange rate to ensure that no impurities in the samples affected the calculations.

Cyclohexyl Compounds. Except for the derivatives listed below, the monosubstituted cyclohexanes were obtained from commercial sources and were purified by preparative vpc or careful fractionation. All compounds gave elemental analysis indicative of satisfactory purity by this criteria.

Cyclohexylacetylene. 1,1-Dichloro-2-cyclohexylethane[50] (10 g) was placed in a 50-cc, round-bottomed flask with 20 g of powdered potassium hydroxide and a magnetic stir bar. The flask was fitted with a fractionation column (30-cm Podbielniak column) and the mixture heated to 165° using an oil bath. The cyclohexylacetylene slowly distilled as the reaction proceeded, yield 3 g. The material was further purified by preparative glpc.

Cyclohexyl tosylate was prepared by the procedure of Brown and Ham.[51]

Cyclohexyl methanesulfonate was kindly supplied by Professor D. S. Noyce.

Trideuteriomethoxycyclohexane. Dry cyclohexanol (50 ml) was treated with 3.9 g (0.06 g-atom) of potassium in chunks and the reaction mixture was warmed slightly until it was apparent that all the potassium had reacted. The solution was allowed to cool, whereupon it solidified. A 15.0-g (0.10 mol) sample of trideuteriomethyl iodide was added in one portion causing the solid mixture to become more mobile. The reaction mixture was stirred at room temperature for 48 hr and filtered (KI) and the crude trideuteriomethoxycyclohexane, bp 130° (756 mm), was isolated by fractionation. The crude product was further purified by preparative glpc on a 20% QF-1 60–80 Chromosorb W column (10 ft × 0.5 in.) at 145° with a helium flow of 120 cc/min. The yield was 2.3 g (30%) of trideuteriomethoxycyclohexane: nmr peaks (60 MHz, CCl_4) at δ 3.06 (1 H multiplet, HCO) and 1.00–2.10 (10 H multiplet). The trideuteriomethoxycyclohexane gave essentially the same glpc retention time (3.6 min at above conditions) as an authentic sample of methoxycyclohexane.

Methyl Cyclohexyl Thioether. A freshly distilled 75-ml portion of cyclohexyl mercaptan (Aldrich Chemical Co., Inc.) was treated with 4.4 g (0.19 g-atom) of sodium in chunks. After dissolution of the sodium metal, the solution was cooled to 0°, and 27.5 g (0.19 mol) of methyl iodide was added slowly. The reaction mixture was allowed to stir overnight and then filtered (NaI) and fractionated on an 18-in. spinning-band column to give 8.3 g (34%) of methyl cyclohexyl thioether: bp 65–66° (8 mm); nmr peaks (60 MHz, CCl_4) at δ 1.00–2.00 (10 H multiplet), 2.03 (3 H singlet SCH_3), and 2.50 (1 H multiplet, methine proton). The thioether was further purified by preparative glpc on a 20% QF-1 60–80 Chromosorb W column (10 ft × 0.37 in.) at 150° with a helium flow of 150 cc/min.

Trideuteriomethyl Cyclohexyl Thioether. The procedure used was exactly analogous to that for the preparation of methyl cyclohexyl thioether except trideuteriomethyl iodide (20 g) was used to give trideuteriomethyl cyclohexyl thioether: bp 63° (7 mm); nmr peaks (60 MHz, CCl_4) at δ 1.00–2.00 (10 H multiplet) and 2.50 (1 H multiplet, methine proton).

Fluorocyclohexane. The method used was that of Grosse and Linn[52] to give fluorocyclohexane, bp 41–42° (81 mm). The fluorocyclohexane was further purified by preparative glpc using a 15% DEGS–15% sodium bicarbonate column (10 ft × 0.5 in.) at 100° with a helium flow of 280 cc/min.

Cyclohexylmercuric acetate was prepared by standard procedures.[53]

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(48) See Table II, footnote *k*.

(49) See Table II, footnote *j*.

(50) Prepared according to the procedure of L. Schmerling, *J. Am. Chem. Soc.*, **71**, 698 (1949).

(51) H. C. Brown and G. Ham, *ibid.*, **78**, 2735 (1956).

(52) A. V. Grosse and C. B. Linn, *J. Org. Chem.*, **3**, 26 (1938).

(53) R. J. Ouellette, Ph.D. Dissertation, University of California, 1961.