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Conformational Properties of Monosubstituted Cyclohexanes in Their Thiourea Inclusion Compounds and in Solution: Variable-Temperature One-Dimensional and Two-Dimensional ^{13}C NMR Investigations

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Abstract: Temperature-dependent changes in high-resolution solid state ^{13}C NMR spectra of thiourea inclusion compounds containing monosubstituted cyclohexane guest molecules ($\text{C}_6\text{H}_{11}\text{X}$; $\text{X} = \text{CH}_3, \text{NH}_2, \text{OH}, \text{Cl}, \text{Br}, \text{I}$) have demonstrated that a "chair–chair" ring inversion process occurs for these guest molecules inside the thiourea tunnel, and the energy barriers for this process have been determined. The relative populations of the axial and equatorial conformers of the guest molecules have been determined directly from the NMR spectra recorded (at low temperature) under slow exchange conditions. On this basis, the guest molecules studied can be divided into two classes: those with $\text{X} = \text{Cl}, \text{Br},$ and I have a predominance of the axial conformer (relative populations of equatorial conformer $\approx 0.05\text{--}0.15$), whereas those with $\text{X} = \text{CH}_3, \text{NH}_2,$ and OH have a predominance of the equatorial conformer (relative populations of equatorial conformer $\approx 0.82\text{--}0.97$). In addition, conformational properties of these monosubstituted cyclohexanes in solution have been reinvestigated via variable-temperature ^{13}C NMR measurements. It is shown, from the reported results for methylcyclohexane, that two-dimensional exchange spectroscopy can successfully identify minor conformers with relative populations as low as 0.01 in solution and 0.03 in the solid state.

Introduction

Thiourea is known to form crystalline inclusion compounds (i.e. host–guest systems)^{1–4} with a range of guest molecules of appropriate size and shape; in these inclusion compounds, the thiourea (host) molecules form an extensively hydrogen-bonded structure which contains uni-directional, non-intersecting tunnels (Figure 1). The monohalogen-substituted cyclohexane/thiourea inclusion compounds are of particular interest since it has been shown^{5–8} that the guest (monohalogen-substituted cyclohexane) molecules are compelled to exhibit uncharacteristic conformational behavior when incarcerated within the thiourea tunnel. For monohalogen-substituted cyclohexanes under certain circumstances, there is equilibrium between the conformations with axial and equatorial orientations of the halogen atom, with a "chair" conformation of the cyclohexane ring in both cases. In the liquid and vapor phases there is an excess of the equatorial conformer,^{9–11} whereas in the solid state at sufficiently low temperature or high pressure they exist only in this conformation.¹² However, when included within the thiourea host tunnel structure, chlorocyclohexane, bromocyclohexane, and iodocyclohexane^{5–8} have been shown to exist predominantly as the axial conformation—these results have been established from IR,^{5,6} Raman,⁷ and high-resolution solid-state ^{13}C NMR⁸ techniques. Similar behavior has been found for other monosubstituted,

trans-1,2-disubstituted, and *trans*-1,4-disubstituted cyclohexanes in their thiourea inclusion compounds.¹³

The cyclohexane/thiourea inclusion compound has been the subject of extensive investigations^{14,15} from the viewpoint of its structural and dynamic properties, including detailed variable-temperature ^2H NMR studies to probe changes in these properties associated with the phase transitions in this inclusion compound. It has been proposed¹⁵ that in the cyclohexane-*d*₁₂/thiourea inclusion compound, structural changes occur, as a result of the phase transitions, which are similar to those reported for the trioxane/urea inclusion compound, although there is no diffraction-based evidence, at present, to substantiate or refute this claim. For trioxane/urea, X-ray diffraction has shown that at room temperature the periodicity of the guest structure along the tunnel axis is twice that of the host structure, whereas below the phase transition temperature (240 K) this periodicity becomes equal to that of the host structure; no further change in the guest periodicity occurs on cooling through the phase transitions at lower temperature, which are believed to be associated with some distortion of the host structure.¹⁶ The cyclohexane-*d*₁₂/thiourea inclusion compound has been investigated in detail via ^2H NMR spectroscopy, which has revealed important insights into the dynamic properties of the guest molecule. For example, these studies have suggested that the activation energy for "chair–chair" ring inversion of the cyclohexane molecule within the thiourea tunnel is *ca.* 46.4 kJ mol^{−1}.¹⁵

In this paper we report variable-temperature high-resolution solid state ^{13}C NMR studies of thiourea inclusion compounds containing guest molecules $\text{C}_6\text{H}_{11}\text{X}$ with $\text{X} = \text{CH}_3, \text{NH}_2, \text{OH}, \text{Cl}, \text{Br},$ and I . The relative amounts of axial and equatorial conformers have been determined directly from the ^{13}C NMR spectra recorded at sufficiently low temperature (i.e. under slow

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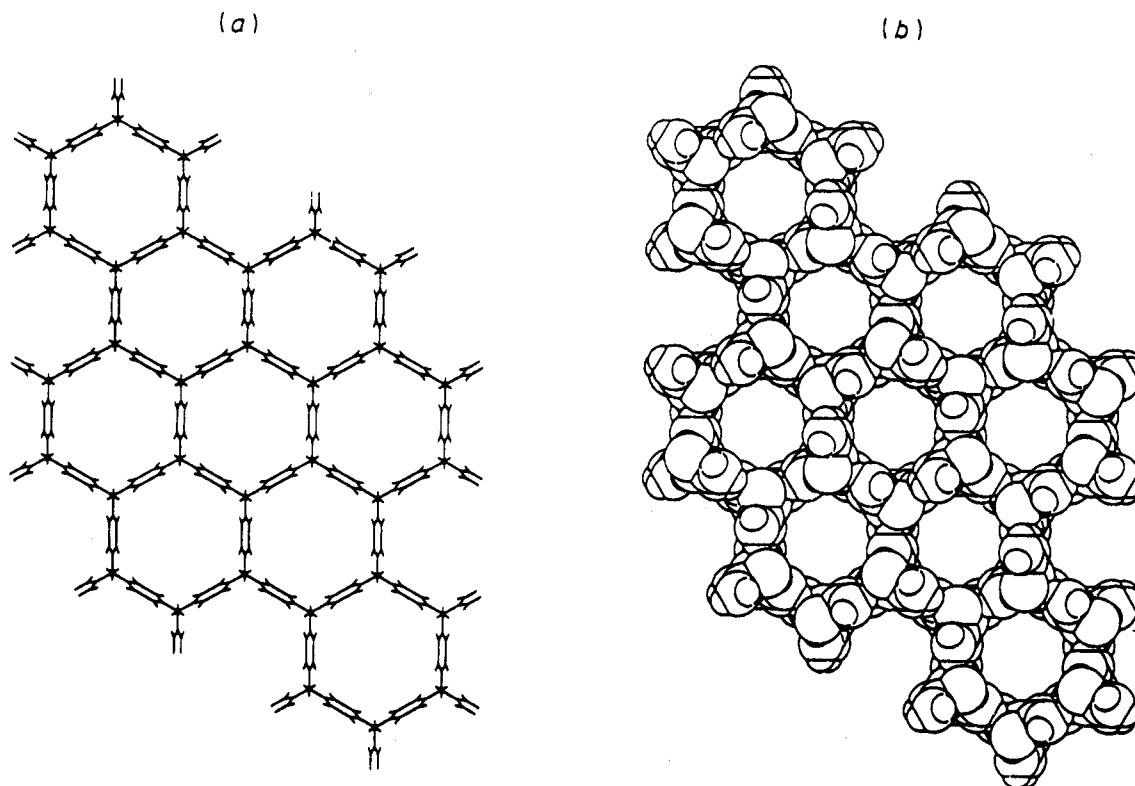


Figure 1. Two representations (showing nine complete tunnels) of the host (thiourea) structure in the $C_6H_{11}Cl$ /thiourea inclusion compound, viewed along the tunnel axis. The atomic radii are zero in representation a, whereas conventional van der Waals radii are used in representation b. The distance from the center of one tunnel to the center of an adjacent tunnel is ca. 9.2 Å. This host structure is stable only when the tunnels are densely packed with guest molecules (not shown).

exchange conditions), and temperature-dependent changes of the line widths in these spectra have been used to probe energetic aspects of the ring inversion process for each of the guest molecules studied. Furthermore, the existence of a chemical exchange process and the exact nature of this exchange process have been investigated via two-dimensional solid-state ^{13}C NMR (^{13}C CP-EXSY) techniques.

For all the monosubstituted cyclohexane molecules discussed above, the conformational properties in solution have been reinvestigated using low-temperature ^{13}C NMR measurements.

Experimental Section

Thiourea inclusion compounds were prepared by slow cooling or slow evaporation of solutions containing the monosubstituted cyclohexane ($C_6H_{11}X$; $X = CH_3, NH_2, OH, Cl, Br, I$) and thiourea dissolved in methanol.⁴ After the crystals were collected, they were washed with 2,2,4-trimethylpentane to remove any $C_6H_{11}X$ molecules adhering to their external surfaces. All samples of thiourea inclusion compounds were characterized by powder X-ray diffraction (verifying that the host structure in these inclusion compounds is the same as that reported previously⁴ for the chlorocyclohexane/thiourea inclusion compound). All reagents and solvents were commercially available and were used without further purification.

^{13}C and 1H solid state NMR spectra were recorded at 125.76 and 500.13 MHz, respectively, on a Bruker MSL500 spectrometer using a standard Bruker magic angle sample spinning (MAS) probe with double-bearing rotation mechanism. The samples were studied as polycrystalline powders in zirconia rotors (4 mm external diameter), and MAS frequencies between 2 and 12 kHz, with stability better than ca. ± 10 Hz, were used. A "single pulse" sequence was used to record the ^{13}C NMR spectra, with inverse-gated 1H decoupling applied during acquisition. Typical operating conditions were the following: ^{13}C 90° pulse length = 3.5 μs ; recycle delay = 2–15 s; number of transients typically between 64 and 10000; 1H decoupler field strength ca. 65 kHz. Two-dimensional ^{13}C CP-EXSY spectra were obtained using the pulse sequence of Szeverenyi *et al.*¹⁷

The digital resolution was ca. 0.5 Hz, and the accuracy of temperature measurements was ca. ± 2 K. Temperature calibration was carried out via experiments on a freshly recrystallized sample of samarium acetate

tetrahydrate¹⁸ and was checked by studying the phase transition temperature of tetrakis(trimethylsilyl)silane (TTMSS).^{19,20} The line widths of the isotropic peaks in the ^{13}C NMR spectra were measured as the full-width at half-maximum height, and the experimental error in the measured line width is estimated to be less than ca. ± 3 Hz. The ^{13}C chemical shifts are given relative to tetramethylsilane (TMS), determined via the use of TTMSS as internal standard. The temperature dependence of the ^{13}C (and ^{29}Si) NMR spectrum of TTMSS has been reported elsewhere.²⁰

All solution state spectra (with concentration ca. 50% v/v) were recorded using a Bruker AM300 NMR spectrometer (75.474 MHz ^{13}C) and a broad-band probe designed for 10-mm-diameter tubes. A mixture of $CDCl_3$ and $CFCl_3$ (1:3 v/v) containing 1% TMS as the chemical shift reference ($\delta = 0$ ppm) was used as the solvent. The room temperature shims were adjusted iteratively, as described by Conover,²¹ by monitoring the deuterium lock signal of 90% benzene in benzene- d_6 . Using a single ^{13}C pulse (length 3 μs , corresponding to ca. 30°) followed by low-power, synchronous, composite pulse proton decoupling via the 96-pulse WALTZ-16 sequence,²² the ^{13}C line width at half-height for benzene was 0.07 Hz. A 1H 90° pulse length of 160 μs was used in the WALTZ-16 sequence. For the solutions studied it was found that, at lower temperatures, shimming using the deuterium lock signal of the solvent ($CDCl_3$) could be misleading and better resolution (with 0.2–0.4 Hz line width of the ^{13}C signal from TMS) was obtained by shimming using the 1H and ^{13}C free induction decays at each temperature with or without deuterium field-frequency lock. In addition, the decoupler power output was adjusted for each sample and for each temperature studied in order to obtain the optimum decoupling field strength. The accuracy of temperature measurements was ± 2 K. The line widths of the peaks in the ^{13}C NMR spectra were determined by Lorentzian line shape fitting, and the

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Table I. ^{13}C NMR Chemical Shifts, δ (ppm), and Line Widths, Δ (Hz), for Monosubstituted Cyclohexane ($\text{C}_6\text{H}_{11}\text{X}$) Guest Molecules in Their Thiourea Inclusion Compounds as a Function of Temperature^a

substituent (X)	T/K	δ /ppm (Δ /Hz)				
		C-1	C-2(6)	C-3(5)	C-4	CH_3
CH_3	208	28.7 [ax] 33.8 [eq]	32.7 [ax] 36.5 [eq]	21.4 [ax] 27.7 [eq]	27.7 [ax] 27.7 [eq]	17.4 [ax] 23.9 [eq]
	223	33.9 (32)	36.6 (39)	27.7 (50)	27.7 (50)	24.1 (24)
	238	33.9 (54)	36.7 (56)	27.8 (59)	27.8 (59)	24.2 (47)
	243	33.9 (72)	36.7 (65)	27.8 (69)	27.8 (69)	24.3 (59)
	248	33.9 (80)	36.6 (73)	27.8 (76)	27.8 (76)	24.3 (90)
	253	33.8 (109)	36.5 (83)	27.9 (94)	27.9 (94)	24.2 (103)
	258	33.6 (110)	36.4 (77)	27.9 (105)	27.9 (105)	24.0 (130)
	274	33.2 (67)	36.2 (53)	27.0 (99)	27.9 (49)	23.6 (91)
	289	33.0 (45)	36.1 (47)	26.7 (67)	27.9 (47)	23.3 (69)
	303	32.4 (19)	35.7 (18)	26.0 (23)	27.9 (16)	22.8 (21)
	323	32.2 (14)	35.7 (17)	25.9 (18)	28.0 (16)	22.7 (16)
	343	32.2 (15)	35.7 (16)	25.9 (20)	28.0 (16)	22.7 (12)
NH_2	208	46.5 [ax] 51.4; 52.6 ^b [eq]	34.2 [ax] 37.2; 38.2 [eq]	20.6 [ax] 26.8 [eq]	26.8 [ax] 26.8 [eq]	
	223	46.5 [ax] 51.5; 52.5 ^b [eq]	34.3 [ax] 37.5; 38.1 [eq]	20.8 [ax] 26.8 [eq]	26.8	
	233	46.5 [ax] 51.4; 52.3 ^b [eq]	37.7 (280)	20.9 [ax] 26.8 [eq]	26.8	
	238	52.2 (200)	37.8 (230)	21.0 [ax] 26.9 (104) [eq]	26.9 (104)	
	243	52.1 (210)	37.8 (220)	27.0 (112)	27.0 (112)	
	248	52.1 (210)	37.8 (209)	27.0 (117)	27.0 (117)	
	258	51.4 (145)	37.6 (154)	26.4	27.1	
	268	51.1 (90)	37.5 (113)	26.1	27.2	
	279	51.1 (73)	37.5 (87)	25.9 (148)	27.2 (68)	
	303	50.7 (80)	37.5 (99)	25.5 (124)	27.3	
	323	50.6 (80)	37.5 (85)	25.3 (107)	27.4	
	343	50.5 (50)	37.5 (58)	25.2 (65)	27.5 (90)	
OH	177	66.6 [ax] 71.9 [eq]	33.3 [ax] 37.1; 36.7 [eq]	20.9; 20.5 [ax] 26.0 [eq]	27.5 [ax] 26.0 [eq]	
	198	66.6 [ax] 71.8 [eq]	33.3; 33.5 [ax] 37.1 [eq]	20.7; 21.0 [ax] 26.2 [eq]	27.5 [ax] 26.2 [eq]	
	218	66.5 [ax] 71.8 [eq]	33.4; 33.6 [ax] 37.1 [eq]	20.8; 21.0 [ax] 26.3 [eq]	27.5 [ax] 26.3 [eq]	
	238	66.7 [ax] 71.7 [eq]	33.8 [ax] 37.2 [eq]	21.2 [ax] 26.3 [eq]	26.3 (112)	
	243	67 [ax] 71.6 (113) [eq]	35 [ax] 37.1 (113) [eq]	21.3 [ax] 26.7 (166) [eq]	26.7 (166)	
	248	71.5 (154)	36.9 (154)	26.3 (246)	26.7	
	253	71.1 (225)	36.7 (146)	25.7 (270)	26.8 (55)	
	263	70.5 (150)	36.5 (91)	25.0 (170)	26.8 (35)	
	279	70.4 (78)	36.3 (43)	24.9 (80)	26.9 (26)	
	303	70.2 (28)	36.3 (28)	24.7 (34)	27.1 (44)	
	323	70.1 (20)	36.3 (25)	24.7 (30)	27.1 (40)	
	343	70.1 (15)	36.4 (21)	24.7 (21)	27.2 (26)	
Cl	159	60.4 [ax] 59.2 [eq]	34.1; 34.7 [ax] 38.9 [eq]	20.4; 20.8 [ax] 28.0 [eq]	26.8 [ax] 26.0 [eq]	
	177	60.4 [ax] 59.2 [eq]	34.2; 34.6 [ax] 38.9 [eq]	20.4; 20.7 [ax] 27.5; 27.9 [eq]	26.8 [ax] 26.0 [eq]	
	208	60.3 (21)	34.7 (36); 39.0	20.6; 20.8	27.0 (20)	
	228	60.3 (25)	34.8 (42)	20.8 (44)	27.0 (26)	
	238	60.3 (22)	34.8 (54)	20.8 (57)	27.0 (25)	
	247	60.3 (19)	35.0 (69)	21.0 (94)	27.0 (19)	
	250	60.3 (18)	35.0 (80)	21.1 (102)	27.0 (19)	
	253	60.3 (17)	35.1 (76)	21.1 (107)	27.1 (18)	
	258	60.3 (17)	35.2 (65)	21.5 (113)	27.1 (16)	
	263	60.4 (16)	35.3 (64)	21.5 (108)	27.1 (16)	
	269	60.4 (16)	35.3 (52)	21.6 (101)	27.1 (18)	
	303	60.5 (16)	35.5 (23)	21.9 (27)	27.1 (24)	
	323	60.5 (16)	35.6 (22)	22.0 (25)	27.2 (25)	
	343	60.6 (15)	35.7 (21)	22.1 (22)	27.2 (25)	
	363	60.6 (13)	35.8 (17)	22.2 (17)	27.2 (20)	
Br	208	55.5 [ax] 50.8 [eq]	35.2; 35.5 [ax] 40.1 [eq]	21.4; 21.8 [ax] 28.9; 29.2 [eq]	27.1 [ax] 26.3 [eq]	
	218	55.4 (25)	35.3; 35.5	21.4 (30); 21.8	27.1 (23)	
	238	55.3 (31)	35.5 (35)	21.7 (56)	27.1 (19)	
	243	55.3 (37)	35.5 (38)	21.7 (59)	27.1 (17)	
	248	55.3 (42)	35.6 (50)	21.7 (64)	27.1 (17)	
	253	55.3 (39)	35.7 (45)	21.7 (69)	27.1 (17)	
	263	55.2 (34)	35.7 (40)	21.9 (66)	27.1 (16)	
	274	55.2 (28)	35.8 (36)	22.0 (61)	27.2 (15)	
	303	55.3 (18)	35.9 (20)	22.1 (25)	27.2 (21)	
	323	55.3 (15)	36.0 (17)	22.3 (20)	27.2 (21)	
	343	55.3 (14)	36.1 (16)	22.4 (16)	27.2 (18)	
	363	55.3 (14)	36.1 (15)	22.5 (16)	27.2 (17)	

Table I (Continued)

substituent (X)	T/K	δ /ppm (Δ /Hz)				
		C-1	C-2(6)	C-3(5)	C-4	CH ₃
I	177	37.8 [ax]	36.9; 37.2 [ax]	22.8; 23.7 [ax]	27.0 [ax]	
		29.3 [eq]	42.0 [eq]	30.0 [eq]	26.2 [eq]	
	208	37.9 (47) [ax]	37.1 (49) [ax]	23.5 [ax]	27.2 (36)	
		29.0 [eq]	42.1 (69) [eq]	30.2 [eq]		
	238	37.9 (32)	37.2 (34)	23.5 (56)	27.3 (28)	
	253	37.9 (52)	37.2 (39)	23.6 (54)	27.4 (28)	
	263	37.7	37.4	23.7 (63)	27.4 (31)	
	278	37.6	37.6	24.0 (110)	27.5 (64)	
	285	36.2	38.3 (102)	24.9 (125)	27.2 (63)	
	299	36.0	38.3 (85)	25.0 (107)	27.2 (65)	
	303	35.5 (84)	38.8 (74)	25.6 (91)	27.2	
	323	35.0 (79)	39.2 (65)	26.1 (75)	27.0	
	343	34.9 (77)	39.4 (60)	26.3 (70)	27.0	

^a Data referring to equatorial and axial conformations are denoted [eq] and [ax], respectively. ^b Two lines with approximate intensity ratio 2:1.

experimental error in the measured line width is estimated to be less than *ca.* ± 0.3 Hz. Temperature calibration was carried out via experiments on pure methanol in a 10-mm-diameter tube.²³ Two-dimensional solution state ¹³C EXSY spectra were obtained using the NOESY pulse sequence²⁴ with ¹H composite pulse decoupling.

Signal area ratios were determined by electronic integration of peaks in the ¹³C spectra (or both ¹H and ¹³C spectra in the case of solution state NMR measurements) with the highest signal-to-noise ratios (>100). The experimental error in the values of the relative population of equatorial conformer measured in this way is estimated, on the basis of the results from 10–50 independent measurements from each spectrum, to be *ca.* $\pm 0.5\%$. Taking into account this value and the accuracy of the temperature measurements (*ca.* ± 2 K), the experimental error in the $-\Delta G^\ddagger$ values (*vide infra*) determined in this work is estimated to be ± 0.07 kJ mol⁻¹. The presence of three exchanging pairs of signals, assigned to C-1, C-3(5), and CH₃, at approximately the same coalescence temperature (258 K) for C₆H₁₁CH₃/thiourea (Table I), allows $\Delta G^\ddagger(\text{ax})$ and $\Delta G^\ddagger(\text{eq})$ (*vide infra*) to be determined independently from three different sets of measurements at this temperature; this permits an assessment of the error in the $\Delta G^\ddagger(\text{ax})$ and $\Delta G^\ddagger(\text{eq})$ values determined here to be *ca.* ± 0.3 kJ mol⁻¹.

Results and Discussion

For all the thiourea inclusion compounds studied in this work, the ¹³C CP-MAS method is less efficient, in terms of sensitivity for carbons of the guest molecules, than the ¹³C “single pulse” method at room temperature. However at low temperatures (160–200 K), corresponding to the slow exchange region (*vide infra*), the CP-MAS method becomes more efficient than the “single-pulse” method.

Figure 2 shows the ¹³C MAS NMR spectra of the C₆H₁₁-OH/thiourea inclusion compound, recorded at various temperatures using the “single pulse” method with ¹H decoupling. At 343 K, relatively narrow resonances with line widths 15–26 Hz are observed; the chemical shifts (Table I) are in good agreement with those expected for the equatorial conformer (on the basis of substituent chemical shift parameters for the hydroxyl group determined from low-temperature solution state NMR studies²⁵ (see also Table II)). On lowering the temperature, spectral changes characteristic of a dynamic exchange process are observed (Figure 2) with large broadening (up to 270 Hz) of lines in the coalescence region ($T \approx 248$ –253 K, depending upon which spectral line is considered). Two groups of signals with approximate integral intensity ratio 4.5:1.0 are readily recognized in the spectra recorded in the range 177–218 K. These subspectra are assigned to the equatorial and axial conformers, respectively.

In the case of C₆H₁₁CH₃/thiourea, a single set of resonances (with line widths 12–20 Hz) is observed for the guest molecule in the high-temperature region. The technique of Zilm and

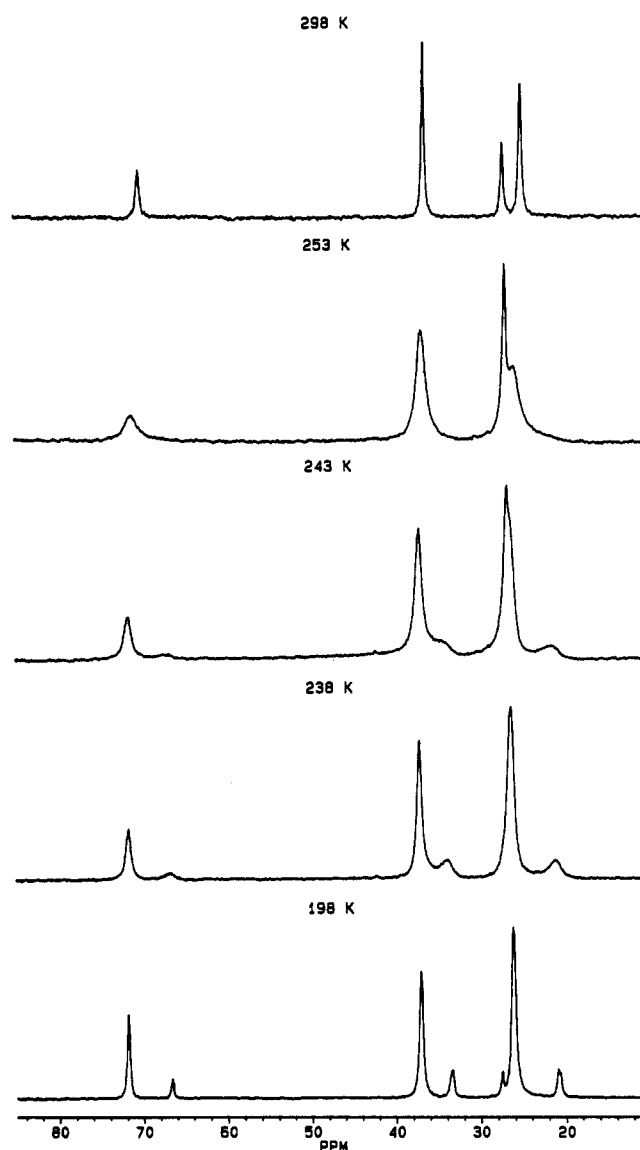


Figure 2. ¹³C MAS NMR spectra of the C₆H₁₁OH/thiourea inclusion compound recorded as a function of temperature showing spectral changes typical for a dynamic two-site exchange process (“chair–chair” ring inversion).

Grant²⁶ has allowed an unambiguous assignment of the resonances in the room-temperature spectrum of this inclusion compound. As for cyclohexanol/thiourea, extreme line-broadening occurs on cooling with a maximum in the line width (Table I) at around 253–258 K; further cooling is associated with line-narrowing,

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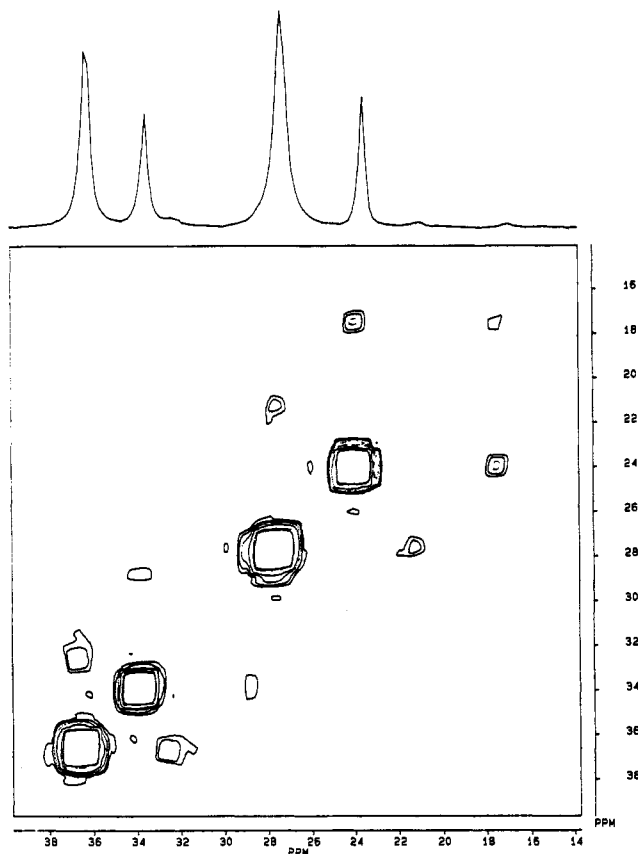
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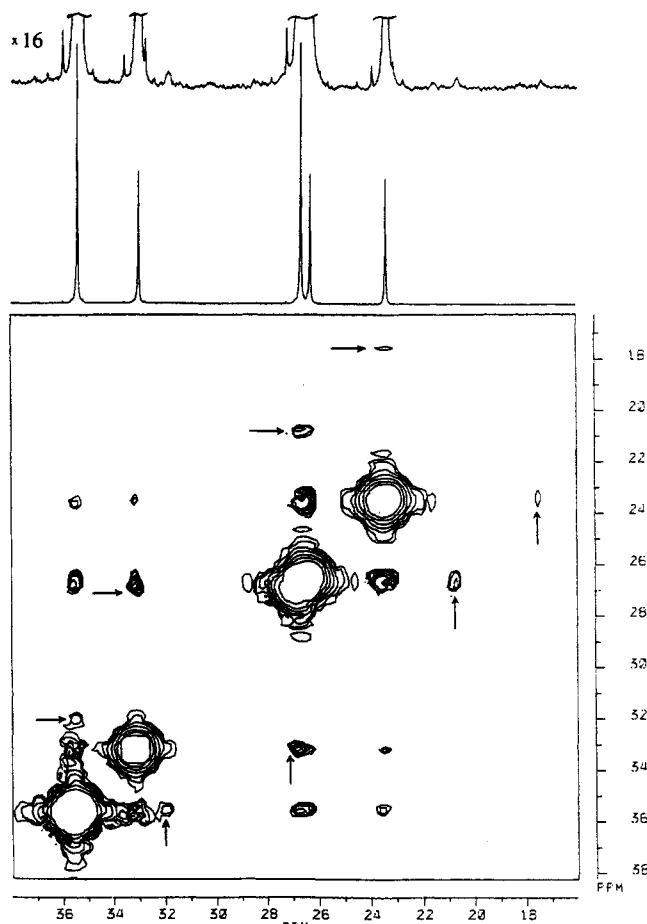
Table II. ^{13}C NMR Chemical Shifts for Monosubstituted Cyclohexanes ($\text{C}_6\text{H}_{11}\text{X}$) in $\text{CFCl}_3/\text{CDCl}_3$ (3:1) Solution^a

substituent (X)	T/K	δ/ppm				
		C-1	C-2(6)	C-3(5)	C-4	CH_3
CH_3 {L}	293	33.33	35.96	26.96	26.81	23.14
CH_3 [eq] {L}	200	33.27	35.66	26.88	26.53	23.48
CH_3 [ax] {L}	200	27.67	32.12	20.85	27.19	17.45
CH_3	293	33.24	35.88	26.86	26.73	23.07
CH_3 [eq]	200	33.11	35.52	26.73	26.36	23.43
CH_3 [ax]	200	27.54	31.97	20.72	27.22	17.44
NH_2	293	50.81	37.33	25.47	26.11	
NH_2 [eq]	200	50.77	36.86	25.69	25.49	
NH_2 [ax]	200	45.49	33.15	19.92	26.5	
OH	293	70.10	35.71	24.65	25.93	
OH [eq]	200	70.31	35.49	24.95	25.42	
OH [ax]	200	65.49	32.49	20.22	26.32	
Cl	293	59.56	37.07	25.12	25.61	
Cl [eq]	200	59.63	37.74	26.69	25.04	
Cl [ax]	200	59.95	33.98	20.20	25.92	
Br	293	52.63	37.66	25.85	25.36	
Br [eq]	200	52.32	38.54	27.72	24.90	
Br [ax]	200	55.38	34.61	20.93	25.79	
I	293	30.82	39.73	27.34	25.47	
I [eq]	220	29.93	40.53	29.04	24.86	
I [ax]	220	37.15	36.06	22.39	25.87	

^a Data for $\text{C}_6\text{H}_{11}\text{CH}_3$ have also been recorded for the neat liquid (denoted {L}).

**Figure 3.** Two-dimensional ^{13}C CP-EXSY spectrum of the $\text{C}_6\text{H}_{11}\text{CH}_3$ /thiourea inclusion compound recorded at 208 K (mixing time = 50 ms).

together with chemical shift changes (see Table I). In the low-temperature spectra, there are three additional very low intensity resonances at 17.4, 21.4, and 32.7 ppm. However, for this sample ^{13}C NMR spectra did not allow an unambiguous identification of the subspectrum corresponding to the axial conformer, and additional experimental evidence for the presence of this conformation is required. [It is noteworthy that analogous difficulties were encountered in investigations of the conformational prop-

**Figure 4.** Two-dimensional ^{13}C CP-EXSY spectrum of $\text{C}_6\text{H}_{11}\text{CH}_3$ in $\text{CDCl}_3/\text{CFCl}_3$ (1:3 v/v) solution recorded at 200 K (mixing time = 500 ms). Exchange cross-peaks are marked by arrows.

erties of neat liquid methylcyclohexane, and the methyl substituent parameters were first obtained²⁷ from analysis of a series of methyl substituted cyclohexanes (the assignments obtained in this way were later confirmed using the cryogenic trapping technique²⁸.) In order to identify and assign signals due to the axial conformation of the guest molecules in the $\text{C}_6\text{H}_{11}\text{CH}_3$ /thiourea inclusion compound, the two-dimensional ^{13}C CP-EXSY spectrum was recorded at 208 K (Figure 3). For the 50 ms mixing period used, the cross-peaks have higher intensities than the auto-peaks corresponding to the minor conformation; this spectrum thus allows the resonances corresponding to the axial conformer to be assigned and also provides direct evidence for the occurrence of the exchange process between the two conformations. In our solution state ^{13}C NMR studies, signals from the axial conformer (with relative population *ca.* 0.01) were also identified from the two-dimensional ^{13}C EXSY spectrum (Figure 4). These examples clearly demonstrate the potential of two-dimensional exchange spectroscopy for investigating dynamic exchange processes even in the unfavorable case in which the relative population of one of the exchanging sites (the minor form) is as low as 0.01–0.03.

The temperature dependence of the ^{13}C MAS NMR spectrum of $\text{C}_6\text{H}_{11}\text{NH}_2$ /thiourea is qualitatively similar to that discussed above for $\text{C}_6\text{H}_{11}\text{CH}_3$ /thiourea (see Table I for quantitative details).

The dynamic behavior determined from the variable-temperature ^{13}C NMR spectra of each of the thiourea inclusion compounds containing $\text{C}_6\text{H}_{11}\text{Cl}$, $\text{C}_6\text{H}_{11}\text{Br}$, and $\text{C}_6\text{H}_{11}\text{I}$ guests is similar but contrasts markedly with the situation for the other guests discussed above. Specifically, the measured ^{13}C chemical shifts indicate a preference for the axial conformation; this is in

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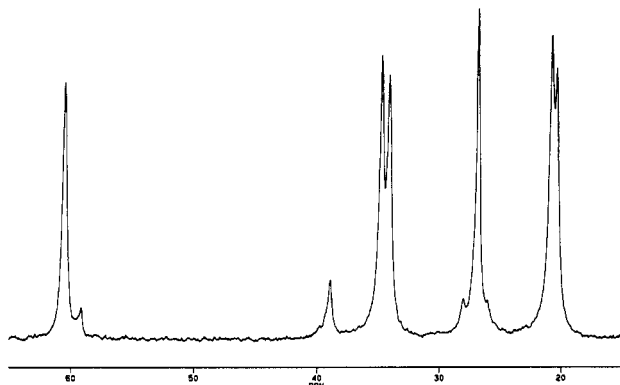


Figure 5. ^{13}C MAS NMR spectrum of the $\text{C}_6\text{H}_{11}\text{Cl}$ /thiourea inclusion compound recorded at 159 K showing the pairs of resonance lines assigned to C-2(6) and C-3(5).

excellent agreement with previous findings from a range of experimental techniques.⁵⁻⁸ For all three monohalogen-substituted cyclohexane guests, all resonances corresponding to the minor equatorial conformer were identified at sufficiently low temperature (in the slow exchange region). For $\text{C}_6\text{H}_{11}\text{Br}$ /thiourea, which is the compound with the lowest proportion of the equatorial conformer, the assignments of the resonances and the presence of the equatorial-axial exchange process were confirmed by the observation of appropriate cross-peaks in the ^{13}C CP-EXSY spectrum recorded at 208 K (mixing time 50 ms).

It should be noted that the ^{13}C NMR spectra of all the thiourea inclusion compounds studied here have a relatively broad resonance (line width ≈ 170 – 200 Hz) at about 180.5 ppm due to the carbon in the thiourea molecule. This chemical shift is different from those reported previously (160 ppm²⁹ and 170 ppm⁸) for thiourea inclusion compounds. Our NMR measurements of pure crystalline thiourea and of thiourea in CDCl_3 solution gave single lines at 181.5 and 184.5 ppm, respectively.

For all of the thiourea inclusion compounds studied, with the exception of $\text{C}_6\text{H}_{11}\text{CH}_3$ /thiourea, two resonance lines corresponding to C-2(6) in the major conformer are observed at sufficiently low temperature (*ca.* 160–230 K)—see Table I and Figure 5. The integrated intensity ratio for these resonance lines is approximately 1:1 in each case, although they generally differ in line width (however, an accurate assessment of line widths is not possible due to the small chemical shift difference between the two resonances). For the inclusion compounds with $\text{C}_6\text{H}_{11}\text{Cl}$ (Figure 5), $\text{C}_6\text{H}_{11}\text{Br}$, and $\text{C}_6\text{H}_{11}\text{I}$ guests at these temperatures, two resonance lines are also observed corresponding to C-3(5) in the major conformer; for $\text{C}_6\text{H}_{11}\text{NH}_2$, and $\text{C}_6\text{H}_{11}\text{OH}$, on the other hand, this cannot be discerned due to overlap of the resonances due to C-3(5) and C-4. In a few cases (see Table I), similar effects are observed for the minor conformer (although, in general, the relatively low population of the minor conformer renders this type of effect difficult to detect). These observations are presumably associated with the occurrence of a phase transition in these inclusion compounds (it has been shown previously,¹⁵ by ^2H NMR, that phase transitions in thiourea inclusion compounds are associated with abrupt changes in the motional freedom of the guest molecules); we are currently investigating structural aspects of these phase transitions in thiourea inclusion compounds.

We now consider the possibility of determination of activation parameters for the exchange process via accurate analysis of the temperature dependence of the line shapes on passing from the slow to fast exchange regions. As noted above, each of the C-2(6) and C-3(5) environments gives rise to more than one resonance in the ^{13}C NMR spectrum at low temperature due to the occurrence of the phase transition. This clearly causes severe difficulties in attempting to perform detailed line shape analysis for the slow-exchange region. In principle, such an approach

could be applied for the intermediate and fast exchange regions. [In making this statement, it should be noted that no spinning sidebands are present in our ^{13}C NMR spectra—analysis of this type, for cases in which spinning sidebands are present, requires consideration of the whole spinning sideband pattern rather than just the isotropic peak.³⁰] The importance of considering the accuracy of activation parameters determined from NMR spectroscopy has been discussed critically in the literature;^{31,32} it has been shown that, for exchanging systems, the precision with which rate constants can be determined from line shape analysis decreases rapidly as the temperature moves away from the coalescence temperature.³¹ Although such a dynamic NMR technique as line shape analysis is suited for a quantitative determination of activation enthalpies and entropies, it has been shown³² that activation entropies of sufficient accuracy for a meaningful chemical interpretation are no longer obtained routinely. This is particularly true for the simple case of exchanging singlets in variable-temperature ^{13}C NMR studies. Taking into account these facts, we preferred not to use such line shape analysis in this work, and a method, described elsewhere,³³ using the coalescence temperature for a pair of lines of unequal intensity to evaluate the free energy of activation was employed in this work. For this analysis, coalescence of the resonance due to the C-2(6) environment was considered for all guest molecules except $\text{C}_6\text{H}_{11}\text{I}$. For $\text{C}_6\text{H}_{11}\text{I}$, coalescence of the resonance due to C-3(5) was considered (since the C-2(6) resonance overlaps with the C-1 resonance (see Table I)).

It is desirable when comparing activation parameters determined from solid state NMR with those determined from solution state NMR that the same method for determining these activation parameters is used in each case. For this reason, we have reinvestigated the conformational properties of the monosubstituted cyclohexane molecules in solution (see Tables II and III) using techniques analogous to those discussed above for the thiourea inclusion compounds.

The conformational ratio and free energies of activation, at the coalescence temperature, for the "chair-chair" ring inversion process have been calculated using this method and are summarized in Table III. We use $\Delta G^*(\text{eq})$ and $\Delta G^*(\text{ax})$ to denote the activation energies from the equatorial and axial conformers, respectively. The values of $\Delta G^*(\text{eq})$ and $\Delta G^*(\text{ax})$ determined for the $\text{C}_6\text{H}_{11}\text{X}$ molecules in solution are in agreement with previous results.³⁴⁻³⁶ For $\text{C}_6\text{H}_{11}\text{CH}_3$, $\text{C}_6\text{H}_{11}\text{NH}_2$, and $\text{C}_6\text{H}_{11}\text{OH}$, the close similarity between the values of $\Delta G^*(\text{eq})$ and $\Delta G^*(\text{ax})$ determined for these molecules in their thiourea inclusion compounds and in solution (Table III) suggests that the thiourea tunnel structure does not exert any significant effect on the relative energies of the equatorial conformation, the transition state, and the axial conformation (i.e. the thiourea tunnel structure exerts a comparable effect on the absolute energies of each of these species). For $\text{C}_6\text{H}_{11}\text{Cl}$, $\text{C}_6\text{H}_{11}\text{Br}$, and $\text{C}_6\text{H}_{11}\text{I}$, on the other hand, there is close similarity between the values of $\Delta G^*(\text{eq})$, but there are significant differences between the values of $\Delta G^*(\text{ax})$, determined for these molecules in their thiourea inclusion compounds and in solution. This suggests that, for these guest molecules, the thiourea tunnel structure exerts a comparable effect on the absolute energies of the equatorial conformation and the transition state, but it exerts a significantly different effect on the absolute energy of the axial conformation. In making these statements, we estimate that differences of about 5 kJ mol⁻¹ or greater in the free energies of activation determined via the technique used here could be confidently assigned as significant.

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Table III. The Relative Population of Equatorial Conformer (p_{eq}), Free Energy Differences ($-\Delta G_T^\circ$), and Free Energy of Activations ($\Delta G^\circ(eq)$ and $\Delta G^\circ(ax)$) of Equatorial and Axial Conformers, Respectively, for the "Chair–Chair" Ring Inversion Process of Monosubstituted Cyclohexanes in Solution and in Their Thiourea Inclusion Compounds (TIC)^a

substituent	p_{eq}	$-\Delta G_T^\circ$, kJ mol ⁻¹	$\Delta G^\circ(eq)$, kJ mol ⁻¹	$\Delta G^\circ(ax)$, kJ mol ⁻¹
CH ₃ (TIC)	0.97	6.0 (208 K)	54 (253 K)	47 (253 K)
CH ₃ (soln)	0.99	7.6 (200 K)	56 (232 K)	44 (232 K)
NH ₂ (TIC)	0.96	4.8 (208 K)	49 (233 K)	43 (233 K)
NH ₂ (soln)	0.98	6.5 (200 K)	52 (235 K)	45 (235 K)
OH (TIC)	0.82	2.5 (198 K)	51 (248 K)	46 (248 K)
OH (soln)	0.96	5.3 (200 K)	50 (233 K)	45 (233 K)
Cl (TIC)	0.08	-3.2 (159 K)	46 (250 K)	51 (250 K)
Cl (soln)	0.81	2.4 (200 K)	48 (240 K)	45 (240 K)
Br (TIC)	0.05	-5.1 (208 K)	46 (248 K)	52 (248 K)
Br (soln)	0.75	1.8 (200 K)	46 (233 K)	44 (233 K)
I (TIC)	0.15	-2.6 (177 K)	52 (285 K)	56 (285 K)
I (soln)	0.76	2.1 (220 K)	48 (249 K)	46 (249 K)

^a All $\Delta G^\circ(eq)$ and $\Delta G^\circ(ax)$ data refer to the coalescence temperature, whereas all $-\Delta G_T^\circ$ data refer to temperatures in the slow exchange region.

The conformational free energy difference $-\Delta G_T^\circ$ between the axial and equatorial conformations is defined as

$$-\Delta G_T^\circ = RT \ln(p_{eq}/p_{ax})$$

Values of $-\Delta G_T^\circ$ determined from our data divide the set of C₆H₁₁X guest molecules in the thiourea inclusion compounds into two classes: those with X = Cl, Br, I have a predominance of the axial conformer ($-\Delta G_T^\circ < 0$; $p_{eq} \approx 0.05$ – 0.15 , where p_{eq} is the relative equatorial population), whereas those with X = OH, NH₂, CH₃ have a predominance of the equatorial conformer ($-\Delta G_T^\circ > 0$; $p_{eq} \approx 0.82$ – 0.97). This issue is discussed further in the next section.

Finally it is noteworthy that, in the low-temperature spectrum of C₆H₁₁NH₂/thiourea, the ¹³C resonance assigned to C-1 of the equatorial conformer is split into a doublet with approximate 2:1 intensity ratio. At the lower fields used in previous studies, similar asymmetric splitting has been attributed to ¹³C–¹⁴N residual dipolar interaction,^{37–39} which is not averaged to zero by MAS (because the axis of quantization of the ¹⁴N nucleus is tilted from the direction of the static magnetic field as a consequence of interaction between the ¹⁴N nuclear quadrupole moment and the electric field gradient at the ¹⁴N nucleus). The line shape and the magnitude of the splitting depend upon the strength of the static magnetic field, the magnitude and sign of the ¹⁴N quadrupole coupling constant, the asymmetry parameter (η), and the carbon–nitrogen internuclear distance (r_{CN}), as well as the angles between the principal axes of the ¹⁴N quadrupole interaction tensor and the vector r_{CN} . The splitting $\Delta\nu$ for a ¹³C nucleus bonded to a ¹⁴N nucleus is expressed^{40,41} as:

$$\Delta\nu = \left(\frac{9D\chi}{20Z_N} \right) (3 \cos^2 \theta - 1 + \eta \sin^2 \theta \cos 2\phi)$$

where $D = \gamma_C \gamma_N \hbar / 4\pi^2 r_{CN}^3$ is the ¹³C–¹⁴N direct dipole–dipole coupling constant, $\chi = e^2 Q q / \hbar$ is the ¹⁴N quadrupolar coupling constant, and $Z_N = \gamma_N \hbar / 2\pi$ is the Larmor frequency. The angles θ and ϕ fix the location of the C–N bond vector in the principal axis system of the electric field gradient tensor at the ¹⁴N nucleus. In the present case, we have $D \approx 0.72$ kHz (obtained using $r_{CN} = 1.45$ Å), and $Z_N = 36.16$ MHz. Estimating the

value of χ for the ¹⁴N nucleus in the C₆H₁₁NH₂ molecule to be ca. 2.0–3.5 MHz,⁴² the maximum possible value of $\Delta\nu$ is estimated (assuming $\eta = 0$ and $\theta = 0$ in the above formula) to be $\Delta\nu_{max} \approx 36$ – 62 Hz. It can be seen that the observed $\Delta\nu$ values given in Table I are larger than this estimated $\Delta\nu_{max}$ by a factor of 2. One possible explanation is that in the high-field case, where the quadrupole interaction is much less than the Zeeman interaction, the situation will be similar to that reported previously⁴³ for ¹³C–²H with $J \approx \Delta\nu$, where J represents the magnitude of the ¹³C–¹⁴N indirect dipole–dipole coupling constant. Under such circumstances, the observed splitting is twice the value predicted on the assumption that J is negligible. However, according to solution NMR data,⁴⁴ the value of $1J(^{13}C, ^{14}N)$ for the C(sp³)–N(sp³) bond does not exceed ca. 5 Hz. Obviously further experimental studies at different applied field strengths (particularly lower field) are desirable, since to our knowledge there have not been any previous reports of the observation of splitting of ¹³C resonances due to ¹³C–¹⁴N residual dipolar interaction at the high magnetic field (11.744 T) used here.

There is substantial narrowing of the ¹H MAS NMR spectra for the thiourea inclusion compounds investigated here (as in the case of zeolite and cyclophosphazene inclusion compounds with various substituted benzenes as the guest.^{45–47}) It has been suggested⁴⁵ that the spin Hamiltonians for such systems have the common feature that all the dipolar interaction tensors have their principal axes in the same direction either because of special features of the crystal structure⁴⁶ or because the whole molecule performs rotational motions which substantially average the intermolecular dipolar interactions.⁴⁷ In the case of thiourea inclusion compounds, the narrow ¹H resonance lines observed for the guest molecules (Figure 6) suggest that the intermolecular dipolar interactions between the host ¹H spins and the guest ¹H spins may be averaged quite substantially as a result of the high conformational, rotational, and translational mobility at room temperature. For C₆H₁₁Br/thiourea (Figure 6) three resolved resonance lines with δ 4.4 (line width at half-height $\Delta\nu_{1/2} = 2.6$ kHz, assigned to H-1), 1.6 ($\Delta\nu_{1/2} = 4.2$ kHz, H-2,3,4) and 8.6 ppm (relatively broad line assigned to ¹H of the thiourea) are observed in the ¹H MAS NMR spectrum.

During preparation of this manuscript, another publication appeared⁴⁸ reporting studies of thiourea inclusion compounds containing methylcyclohexane, chlorocyclohexane, and bromocyclohexane guests by line-shape analysis of variable-temperature ¹³C MAS NMR spectra. However, the presence of both conformers was observed directly only in the case of chlorocyclohexane at low temperature. For bromocyclohexane and methylcyclohexane guests, chemical shifts and relative populations of the minor conformations were predicted via line-shape simulations. Comparison of our data with those reported in ref 48 indicates that the relative populations of conformers determined by the contrasting methods for chlorocyclohexane and bromocyclohexane are in agreement to within $\pm 1\%$ and encourages the use of high-resolution solid state ¹³C NMR techniques for the study of conformational equilibria of molecularly confined systems in the solid state.

Concluding Remarks

The work reported here has demonstrated clearly that monosubstituted cyclohexane molecules embedded within the tunnel

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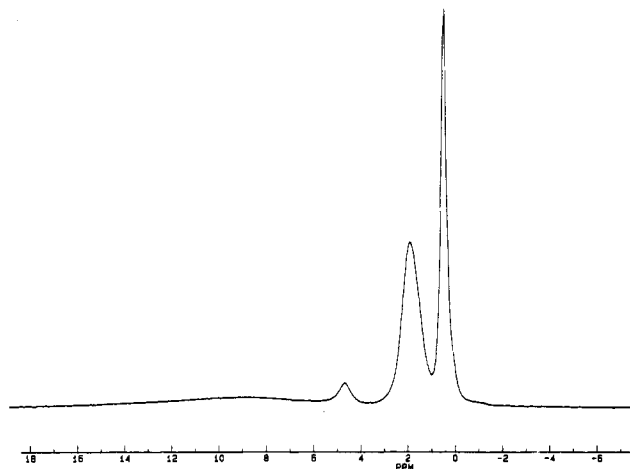


Figure 6. ^1H MAS NMR spectra of the $\text{C}_6\text{H}_{11}\text{Br}$ /thiourea inclusion compound recorded at 293 K (MAS frequency = 10.3 kHz).

structure of their thiourea inclusion compounds can exhibit conformational behavior that contrasts markedly with that of the same molecules in other phases. The work has also provided direct evidence showing that there is dynamic exchange between the axial and equatorial conformations of these guest molecules within the thiourea tunnel structure. Furthermore, it has been demonstrated directly that there are major conformational differences within the set of guest molecules $\text{C}_6\text{H}_{11}\text{X}$ studied, depending upon the identity of the substituent X. It is clear that the dramatic dependence of these properties on the identity of the substituent X reflects the fine and subtle energetic balances that exist for these inclusion compounds, and we now consider this matter in more detail.

The energetics of inclusion compounds, such as the thiourea inclusion compounds discussed here, can, assuming a fixed and known host structure, be considered in terms of three contributions: the energy of host–guest interaction, the energy of guest–guest interaction, and the intramolecular potential energy of the guest molecules. In general, all of these contributions will vary as the conformation of the guest molecule within the inclusion compound is changed. To a good approximation, inclusion compounds in which the host structure comprises uni-directional tunnels can be considered as one-dimensional, and the methodology developed recently^{49–51} for considering energetic aspects of strictly one-dimensional inclusion compounds can be applied to such systems. We summarize this methodology briefly here. Consider a one-dimensional inclusion compound in which the periodicity of the host structure is c_h and in which this host structure is known and assumed to be independent of the structural properties of the guest molecules within it. Within this host, the guest structure consists of n identical guest molecules regularly arranged with periodicity c_g . For such a one-dimensional inclusion compound, it has been shown⁴⁹ that the structural properties of the guest molecules can be predicted and rationalized by minimizing the characteristic energy ($\hat{E}(\alpha, n)$) of the inclusion compound, which is given by:

$$\hat{E}(\alpha, n) = \frac{1}{\alpha} \left[\inf_{\lambda} \left\{ \frac{1}{n} \sum_{k=0}^{n-1} E_h(k\alpha + \lambda) \right\} + \hat{E}_{\text{guest}}(\alpha) + \hat{E}_{\text{intra}} \right]$$

where we now define the guest periodicity as $\alpha = c_g/c_h$; $E_h(t)$ is the energy of a guest molecule, at position t in the host tunnel, due to host–guest interaction; $\hat{E}_{\text{guest}}(\alpha)$ is the guest–guest interaction energy, per guest molecule, when the guest structure has periodicity α ; \hat{E}_{intra} is the intramolecular potential energy for each guest molecule; and λ denotes the position of the first guest

molecule along the tunnel. This methodology has been applied successfully⁵¹ to predict the optimum guest periodicity (α) for alkane/urea inclusion compounds assuming the known urea host structure, and assuming that all guest molecules exist in the all-anti conformation.

Extending this approach to allow a comparison of the relative energetic favorability of two different conformations of a given guest molecule within the inclusion compound (such as comparing the axial and equatorial conformations of the monosubstituted cyclohexanes discussed here) will clearly require the characteristic energy at the optimum α for one conformation of the guest to be compared with the characteristic energy at the optimum α for the other conformation of the guest. While it is obvious that \hat{E}_{intra} will depend critically on the conformation of the guest molecules, it is important to stress that $\hat{E}_{\text{guest}}(\alpha)$ and $E_h(t)$ will, in general, also depend on the conformation of the guest molecules; for these reasons, any qualitative attempt to rationalize the differences in conformational behavior observed for the different guest molecules in the thiourea inclusion compounds discussed here must be approached with caution. With this in mind, we attempt a guarded justification of the experimental results reported in this paper. It is important to note that the factor $1/\alpha$ in the expression for the characteristic energy ensures that the characteristic energy refers to an energy per unit length of host tunnel rather than an energy per guest molecule, and this is undoubtedly a critical factor underlying the preference for the axial conformation of the monohalogen-substituted cyclohexane guest molecules in their thiourea inclusion compounds. Thus, while the equatorial conformation corresponds to a more negative \hat{E}_{intra} than the axial conformation, the guest molecules in the axial conformation can be packed much more efficiently (smaller α) within the thiourea tunnel therefore giving a more favorable host–guest interaction energy, *per unit length of tunnel*, for the axial conformation. This latter contribution presumably outweighs the former contribution in the case of the $\text{C}_6\text{H}_{11}\text{X}$ guest molecules with $\text{X} = \text{Cl}$, Br , and I . For the guest molecules $\text{C}_6\text{H}_{11}\text{X}$ with $\text{X} = \text{CH}_3$, NH_2 , and OH , on the other hand, the difference in \hat{E}_{intra} between the axial and equatorial conformations is known⁵² to be significantly higher than it is for the halogen substituents X (in the cases with $\text{X} = \text{OH}$ and NH_2 , it has also been proposed^{53–55} that, in solution, the formation of hydrogen-bonded dimers also serves to stabilize the equatorial conformation relative to the axial conformation). Thus, in the case of $\text{X} = \text{CH}_3$, NH_2 , and OH , the energy advantage provided by the ability to pack the axial guest molecules more efficiently within the thiourea tunnel is presumably insufficient to outweigh the intramolecular energetic disadvantage of the guest molecule adopting the axial conformation. [It should be stressed that the above discussion has neglected the fact that the potential energy functions E_h and \hat{E}_{guest} will differ for the axial and equatorial conformations of the guest molecules, and this fact must be taken into account in a rigorous analysis of the energetics of these systems.] We are currently undertaking theoretical studies to confirm these proposals; specifically, the methodology discussed above (see ref 51) is being applied, using computed potential energy functions for the $\text{C}_6\text{H}_{11}\text{Cl}$ /thiourea inclusion compound, in order to assess whether structural predictions based on a consideration of the characteristic energy for this inclusion compound do indeed reproduce the experimental conformational properties reported in this paper.

In view of the detailed conformational and dynamic information reported in this paper, a similar solid state NMR approach is now being applied to probe the conformational properties of other cyclohexane-based guest molecules, and other small cyclic guest molecules, in their thiourea inclusion compounds, as well as to

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investigate the conformational properties of $C_6H_{11}X$ guest molecules within other crystalline host materials. The results from these investigations will represent an important step forward in the pursuit of a detailed understanding of the ways in which the properties of molecules embedded within different solid state

environments can be influenced by the structural attributes (or other features) of their environment.

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