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The Conformational Analysis of Saturated Heterocycles. 77.[1] Rationalization of the Equilibria of Tetraalkylhexahydro-1,2,4,5-tetrazines

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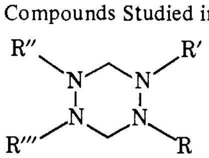
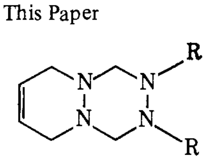
Abstract: Seven monocyclic, four bicyclic, and two tricyclic hexahydro-*s*-tetrazines, including specifically deuterated derivatives, have been studied by ^{1}H NMR, ^{13}C NMR, and other physical techniques. The conformational equilibria are elucidated in terms of four types of conformer (tetraequatorial, triequatorial-monoaxial, and two alternative diequatorial-diaxial), which form three sets equilibrating rapidly at medium temperatures. Conformational preferences are explained in terms of steric, electronic, and entropy effects, and a rational picture of the conformational equilibria in the series is presented.

In an earlier paper[2] we clarified the conformational equilibria of tetramethyl- and tetraethylhexahydrotetrazines (**1**, **2**) together with those of one bicyclic (**10**) and three tricyclic analogues (**14–16**). At that time it was not possible to rationalize the equilibria. We have now studied a considerable number of further compounds (cf. Scheme I), which allows firmer conclusions regarding the factors determining conformational preferences in hexahydrotetrazines. We have also applied ^{13}C NMR to the compounds previously studied. Our earlier paper[2] summarized the previous work up to 1973. Since then the full x-ray structure of hexahydro-1,4-dimethyl-*s*-tetrazine has been published:[3] it exists as the di-Me-equatorial di-H-axial form, but there is evidence for the occurrence of nonsymmetrical isomers in solution.[4]

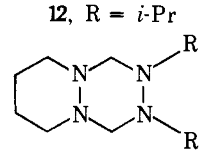
Scheme I. Compounds Studied in Ref 2 and This Paper



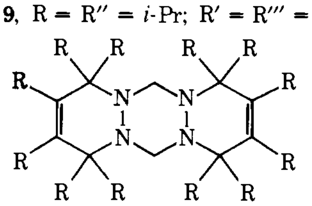
1, R = R′ = R″ = R‴ = Me
2, R = R′ = R″ = R‴ = Et
3, R = R′ = R″ = R‴ = *i*-Pr
4, R = R′ = R″ = R‴ = CH_2Ph
5, R = R″ = Me; R′ = R‴ = CH_2Ph
6, R = R″ = Me; R′ = R‴ = CHDPh
7, R = R‴ = Me; R′ = R″ = CH_2Ph
8, R = R‴ = Me; R′ = R″ = CHDPh
9, R = R″ = *i*-Pr; R′ = R‴ = CH_2Ph



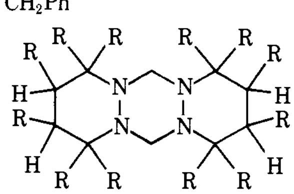
10, R = Me
11, R = Et
12, R = *i*-Pr



13, R = Me



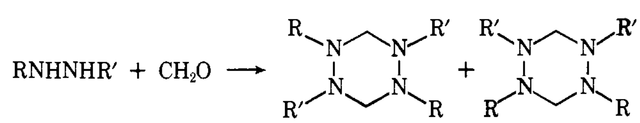
14, R = H
15, R = D



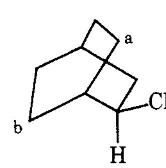
16, R = H
17, R = D

Preparation of Compounds. 1,2,4,5-Tetrasubstituted hexahydro-1,2,4,5-tetrazines in which all the substituents are identical are easily prepared from the appropriate 1,2-disubstituted hydrazine with formaldehyde;[5–7] difficulties in the procedure have been discussed in terms of the mechanism.[8,9] By this method we prepared the new tetrabenzyl compound **4**. From unsymmetrical 1,2-disubstituted hydrazines and formaldehyde, two products **18** and **19** could be formed: in the

Scheme II



18 **19**



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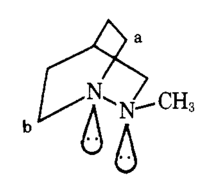

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methyl/benzyl series we isolated both products (**5** in pure form, **7** somewhat contaminated with **5**), in the isopropyl/benzyl series we obtained only the symmetrical product **9**. The specifically deuterated compounds **6** and **8** were prepared similarly from the deuterated hydrazine (MeNHNHCHDPh). Previously, unsymmetrical hydrazines of type PhNHNHR (R = Me, Et, *i*-Pr) have been condensed with formaldehyde[10,11] to give presumably mixed products; isomer determination was not attempted by these workers.

We previously[2] reported the preparation of the bicyclic compound **10**: analogues **11**, **12**, and **13** were prepared similarly. The deuterated tricyclic compound **17** was prepared by hydrogenation of **15**.

Experimental Section

The following compounds were prepared by the literature methods shown: hexahydro-1,2,4,5-tetramethyl-1,2,4,5-tetrazine[5] bp 58–60 °C (11 mm) [lit.[5] bp 58–60 °C (11 mm)]; 1,2,4,5-tetraethylhexahydro-1,2,4,5-tetrazine[12] mp 19–21 °C [lit.[2] mp 19–21 °C]; hexahydro-1,2,4,5-tetraisopropyl-1,2,4,5-tetrazine[5] mp 56–58 °C [lit.[5] mp 57–58 °C]; 6*H*,13*H*-1,4,8,11-tetrahydrobis(pyridazino[1,2-*a*;1',2'-*d*]-*s*-tetrazine)[12] mp 151° [lit.[12] mp 151–152.5 °C]; 6*H*,13*H*-octahydrobis(pyridazino[1,2-*a*;1',2'-*d*]-*s*-tetrazine)[13] mp 170–171 °C [lit.[13] mp 168–169 °C].

1,2,4,5-Tetrabenzylhexahydro-1,2,4,5-tetrazine (4). 1,2-Dibenzylhydrazine (1.2 g, 5.7 mmol) and formaldehyde solution (37%, 1 ml, 12 mmol of H_2CO) were stirred at 25 °C for 1 h. The resulting solid was dissolved in ether and dried (K_2CO_3). After removal of ether the residue recrystallized from benzene-hexane (1:3) to give the *hexahydrotetrazine* as needles (1.0 g, 80%) mp 160–161 °C. Anal. Calcd for $C_{28}H_{32}N_4$: C, 80.3; H, 7.2; N, 12.5. Found: C, 79.8; H, 7.2; N, 12.3.

2,5-Dibenzylhexahydro-1,4-dimethyl-1,2,4,5-tetrazine (5) and 2,4-Dibenzylhexahydro-1,5-dimethyl-1,2,4,5-tetrazine (7). 2-Benzyl-1-methylhydrazine (9 g, 66 mmol) and aqueous formaldehyde (37%, 5.5 ml, 66 mmol of H_2CO) were stirred at 25 °C for 1 h. The resulting solid was fractionally crystallized four times from hexane to yield prisms of the symmetrical *hexahydrotetrazine* (**5**) mp 70–71 °C (3.7 g, 19%). Anal. Calcd for $C_{18}H_{24}N_4$: C, 72.9; H, 8.2; N, 18.9. Found: C, 73.2; H, 8.1; N, 19.0. The less symmetric isomer (**7**) was separated from the mother liquors by repeated preparative TLC (25 × 50 cm plate; eluent chloroform + 5% methanol) and characterized by NMR spectrum; it could not be obtained entirely free from the more symmetric isomer (**5**) (0.2 g, 1%).

2,5-Dideuteriobenzylhexahydro-1,4-dimethyl-1,2,4,5-tetrazine (6) and 2,4-Dideuteriobenzylhexahydro-1,5-dimethyl-1,2,4,5-tetrazine (8). These compounds were prepared as a mixture and separated by TLC in exactly the same way as above for the undeuterated compounds but using 2-deuteriobenzyl-1-methylhydrazine as starting material. The latter was obtained as follows: deuteriodiborane from the cautious addition of 8.2 ml of boron trifluoride diethyl etherate to lithium aluminum deuteride (0.5 g) in ether (7 ml) was swept by a current of nitrogen into a THF (40 ml) solution of benzaldehyde methylhydrazone (0.82 g, 6 mmol). After 10 min HCl gas was passed in to liberate the hydrazine monohydrochloride as a solid. The free hydrazine was obtained by treatment with KOH and extraction into chloroform and characterized by the NMR spectrum. Yield of hydrochloride, 0.64 g (59%).

2,5-Dibenzylhexahydro-1,4-diisopropyl-1,2,4,5-tetrazine (9). To 1-benzyl-2-isopropylhydrazine hydrochloride (5.21 g, 22 mmol) in water (11 ml) was added KOH (2.46 g, 4 N solution) with ice cooling under nitrogen and then, dropwise, aqueous formaldehyde (37%, 1.8 ml, 22 mmol of H_2CO). The mixture was stirred for 12 h, extracted with 3 × 15 ml of Et_2O, dried (K_2CO_3), and evaporated at 60 °C (15 mm). The *hexahydrotetrazine* remaining crystallized from petroleum ether as prisms (2.4 g, 31%), mp 103–105 °C. Anal. Calcd for $C_{22}H_{32}N_4$: C, 74.9; H, 9.2; N, 15.9. Found: C, 74.2; H, 8.8; N, 15.8.

7,8-Diethyl-1,4,6,7,8,9-hexahydropyridazino[1,2-*a*]-*s*-tetrazine (11). Crude 1,2,3,6-tetrahydropyridazine [obtained by hydrolysis of diethyl 1,2,3,6-tetrahydropyridazine-1,2-dicarboxylate[14] (6.84 g, 40 mmol)] was mixed with 1,2-diethylhydrazine (2.64 g, 30 mmol). Aqueous formaldehyde (37%, 7 ml, 86 mmol of H_2CO) was added and the mixture was stirred 10 h at 25 °C. Volatiles were removed at 60 °C (15 mm) and the residue taken up in ether, filtered through anhydrous K_2CO_3, and evaporated. Solid was filtered off and the liquid distilled to give the *hexahydrotetrazine* as an oil (0.9 g, 15%), bp 85–87 °C (2 mm). Anal. Calcd for $C_{10}H_{20}N_4$: C, 61.2; H, 10.3; N, 28.5. Found: C, 61.0; H, 10.1; N, 28.3.

3,4,5,6,7,8,9,10-Octahydro-7,8-dimethylpyridazino[1,2-*a*]-*s*-tetrazine (13). 1,2-Dimethylhydrazine dihydrochloride (12.0 g, 90 mmol) followed by crude hexahydropyridazine (16.1 g, 70 mmol) [obtained by hydrolysis of diethyl hexahydropyridazine-1,2-dicarboxylate[14]] and aqueous formaldehyde (37%, 8 ml, 98 mmol H_2CO) were added at 20 °C to NaOH (6.0 g, 150 mmol) in water (100 ml). The mixture was stirred 10 h at 25 °C. The water and unreacted formaldehyde were removed at 60 °C (15 mm). The residue was taken up in ether, washed (100 ml of saturated $NaHCO_3$), and filtered through anhydrous K_2CO_3. Distillation gave the *hexahydrotetrazine* which solidified in the condenser. Vacuum sublimation and recrystallization (hexane) yielded prisms (0.5 g, 3.8%), mp 47–48 °C. Anal. Calcd for $C_8H_{18}N_4$: C, 56.4; H, 10.7; N, 32.1. Found: C, 56.2; H, 10.5; N, 31.9.

1,1,2,3,4,4,8,8,9,10,11,11-Dodecadeuterio-6*H*,13*H*-octahydrodipyridazino[1,2-*a*;1',2'-*d*]-*s*-tetrazine (17). The perdeuterated tricyclic tetrazine (0.19 g, 1 mmol) (**15**)[2] was shaken under hydrogen in a Cook low pressure hydrogenator with 5% Pd–C catalyst at 25 °C for 4 h. Evaporation gave the *product* as an oil (0.17 g, 85%) which was characterized by the NMR spectrum.

1,4,6,7,8,9-Hexahydro-7,8-diisopropylpyridazino[1,2-*a*]-*s*-tetrazine (12). Crude 1,2,3,6-tetrahydropyridazine (3.36 g, 40 mmol), 1,2-diisopropylhydrazine (3.87 g, 33 mmol), and aqueous formaldehyde (37%, 4 ml, 50 mmol of H_2CO) were stirred 10 h at 25 °C. Volatiles were removed at 60 °C (15 mm) and the residue was taken up in ether, filtered through anhydrous K_2CO_3, evaporated, and distilled. The fraction distilling at 150–154 °C (6 mm) partially solidified on standing, the solid proving to be the tricyclic compound (**14**). The residual oil was subjected to preparative TLC (25 × 50 cm silica plate; eluent chloroform + 5% methanol). One band (R_f ca. 0.6) proved to contain its crude product as an oil on extraction (chloroform) and evaporation. The oil crystallized on cooling and the solid was recrystallized from *n*-hexane, yielding the *hexahydrotetrazine*, as needles, mp 136–142 °C (0.5 g, 6.7%). Anal. Calcd for $C_{12}H_{24}N_4$: C, 64.3; H, 10.7; N, 25.0. Found C, 64.1; H, 10.9; N, 25.5.

Physical Measurements. The ^1H NMR spectra were measured with Varian HA-100 and HR-220 spectrometers. Temperatures were measured by the use of methanol shift down to −90 °C; an improved version of the Varian calibration curve was employed.[15] Below −90 °C, a platinum resistance thermometer set into the low temperature probe was used; this was checked by comparison with a copper–constantan thermocouple mounted in an NMR tube and found to be in agreement ±1 °C. ^{13}C NMR spectra were obtained on a Varian XL-100 machine operating at 25.16 MHz employing an internal deuterium lock in 12 mm tubes. Dipole moments were measured in cyclohexane or benzene at 25 °C by the standard technique.[16] Ir spectra of the liquid samples between NaCl plates were recorded using a Perkin-Elmer Model 125 spectrophotometer at spectral slit widths of ca. 1.2 cm^{-1} using an RIIK variable temperature cell VLT-2. The Raman spectrum of the liquid sample was recorded on a Spex 1401 double monochromator with a 6328 He–Ne laser. Scattering from the sample placed in the cylindrical holder was veiwed perpendicularly to the laser beam by the monochromator. Spectral slit width was ca. 13 cm^{-1}.

Discussion

1,2,4,5-Tetramethylhexahydro-*s*-tetrazine (1). We have previously discussed this compound in detail, summarized the conflicting literature evidence,[12,17] and concluded[2] from proton NMR evidence (Table I), supported by vibrational spectra and dipole moments, that it exists in set III. The ^{13}C NMR spectrum (Table II) at 36 °C shows singlets at δ 70.6 (N–*C*–N) and δ 40.0 (N–*C*) (areas not in the expected ratio due to differing NOE). At −90 °C the N–*C*–N signal remains as a singlet δ 69.6 but the N–*C* peak splits into two approximately equal singlets at δ 40.8 and 40.0; this behavior is consistent only with set III, confirming the previous[2] conclusions: set I is ruled out completely, and set II could account for the behavior only if the lower "non-passing" barrier were slowed. The observed barrier of 11.8 ± 0.2 kcal mol^{-1} is too high for this. Recent photoelectron spectroscopic evidence is in good agreement with these conclusions.[18]

Neither the ^1H nor the ^{13}C spectra show any further significant change down to −150 °C; this indicates that of the individual conformers of set III either (a) only W is populated, or (b) the chemical shift differences are too small for resolution (unlikely for ^{13}C), or (c) the nonpassing barrier is too low for detection. We later give reasons for now believing that conformer W predominates considerably over Z in set III, in contrast to our previous conclusion[2] from chemical shifts that W:Z was 30:70.

1,2,4,5-Tetraethylhexahydro-*s*-tetrazine. We have also previously[2] considered **2** in detail, discussed the literature

Table I. ^{1}H NMR Data of Hexahydrotetrazines

Compd						
No.	Ring	Substituent	Temp, °C	Solvent	Set	Peak assignment and chemical shift[a] pattern
1	Mono	Me_4	20	$CDCl_3 + CFCl_3$	Eqm	CH_3, 2.48 (s); NCH_2N, 3.52 (s)
			−80	$CDCl_3 + CFCl_3$	III	CH_3, 2.49 (s), 2.10 (s); NCH_2N, 3.97, 3.33 (ABq)[b]
2	Mono	Et_4	34	$CDCl_3 + CFCl_3$	Eqm	CH_3, 1.02 (t, 7 Hz); NCH_2C, 2.48 (q, 7 Hz); NCH_2N, 3.82 (s)
			−80	$CDCl_3 + CFCl_3$	II	CH_3, 1.0 (m);[c] NCH_2C, 3.2, 2.81 (ABq); NCH_2N, 4.88, 3.2 (ABq)
			−80	$CDCl_3 + CFCl_3$	III	CH_3, 1.0;[c] NCH_2C, 3.91, 3.61 (ABq); 3.2, 2.35 (ABq), NCH_2N, 3.93, 3.62 (ABq)[d]
3	Mono	*i*-Pr_4	34	$CDCl_3 + CFCl_3$	Eqm	CH_3, 1.01 (d, 6 Hz); CH, 3.32 (septet, 6 Hz); NCH_2N, 3.88 (s)
			−70	CF_2Cl_2	I	CH_3, 1.05 (m);[e] CH, 3.36 (m);[c] NCH_2N, 4.0, 3.8 (ABq)
			−70	CF_2Cl_2	III	CH_3, 1.05 (m);[e] CH, 3.36 (m);[c] NCH_2N, 4.0, 3.8 (ABq)
4	Mono	Bz_4	34	$CDCl_3 + CFCl_3$	Eqm	NCH_2N, 3.76 (s); NCH_2Ar, 3.98 (s); Ar, 7.16 (s)
			−80	CF_2Cl_2	II	NCH_2N, 4.25, 3.09 (ABq); NCH_2Ar, 4.24, 3.76 (ABq); Ar, 7.2
5	Mono	Me_2Bz_2; sym	20	$CDCl_3 + CFCl_3$	Eqm	CH_3, 2.21 (s); NCH_2N, 3.39 (s); NCH_2C, 3.64 (s); Ar, 7.28 (m)
			−80	$CDCl_3 + CFCl_3$	II	CH_3, 2.68;[f] NCH_2N,[g] 4.50, 3.75 (ABq);[h] NCH_2C,[g] 4.06, 3.16 (ABq);[i] Ar, 7.32 (m)
			−80	$CDCl_3 + CFCl_3$	III	CH_3, 2.43, 2.66 (2s);[j] NCH_2N, 3.93, 3.26 (ABq),[k] 4.25, 4.13 (ABq);[k] NCH_2C, 4.38, 3.39 (ABq),[l] 4.06, 3.13 (ABq);[l] Ar, 7.32 (m)
7	Mono	Me_2Bz_2; unsym	34	$CDCl_3 + CFCl_3$	Eqm	CH_3, 2.29 (s); NCH_2N, 3.39, 3.25 (2s); NCH_2C, 3.46 (s)
			−80	$CDCl_3 + CFCl_3$	II and III[m]	CH_3, 2.80 (s), 2.47 (s), 2.41 (s); NCH_2N, 4.39, 4.00 (ABq)[g] 3.83, 3.26 (ABq), 3.41, 3.12 (ABq); NCH_2C, 4.0–4.3, 3.67
9	Mono	Bz_2-*i*-Pr_2; sym	34	$CDCl_3 + CFCl_3$	Eqm	CH_3, 0.97 (d, 7 Hz); CH, 3.04 (septet, 7 Hz); NCH_2N, 3.79 (s); NCH_2Ar, 4.11 (s); Ar, 7.25 (m)
			−80	$CDCl_3 + CFCl_3$	III	CH_3, 1.07, 1.20, 1.25, 1.34 (all d, 7 Hz); CH, 3.65 (m); NCH_2N, 3.79, 3.63 (ABq); 3.66, 3.62 (ABq); NCH_2C, 4.50, 4.40 (ABq), 4.19, 3.98 (ABq); Ar, 7.5 (m)
10	Bi	Me_2; unsat	25	$CDCl_3 + CFCl_3$	Eqm	CH_3, 2.71 (s); NCH_2C, 3.02 (s); NCH_2N; 3.58 (s); CH, 5.7 (s)
			−60	$CDCl_3 + CFCl_3$	VII	CH_3, 2.71 (s); NCH_2C, 2.95, 3.10 (ABq); NCH_2N, 4.04, 3.47 (ABq); CH, 5.70 (s)
11	Bi	Et_2; unsat	34	$CDCl_3 + CFCl_3$	Eqm	CH_3, 1.09 (t, 6 Hz); NCH_2CH_3, 3.6 (m);[c] NCH_2CH, 3.6 (bs);[c] NCH_2N, 2.96 (s)
			−80	$CDCl_3 + CFCl_3$	VII	CH_3, 1.15 (t, 6 Hz); NCH_2CH_3, 3.6 (m); NCH_2CH, 3.25, 2.78 (ABq); NCH_2N, 3.13, 2.94 (ABq); CH, 5.77 (s)
12	Bi	*i*-Pr_2; unsat	34	$CDCl_3 + CFCl_3$	Eqm	CH_3, 0.99 (d, 7 Hz); CH, 2.42 (septet, 7 Hz); NCH_2C, 2.48 (m); NCH_2N, 3.61 (s); vinyl, 5.67 (s)
			−40	$CDCl_3 + CFCl_3$	VII	CH_3, 0.97 (d, 6 Hz); 1.01 (d, 6 Hz); CH, 2.41 (m); NCH_2C, 2.80 (m); NCH_2N, 3.65, 3.62 (ABq); vinyl, 5.79 (bs)
13	Bi	Me_2; sat	−70[n]	$CDCl_3 + CFCl_3$	VII	CH_3, 2.78 (s); CCH_2C, 1.7 (m); NCH_2C, 2.62, 2.23 (ABq); NCH_2N, 3.28, 3.97 (ABq)
14	Tri	Unsat	90[o]	DMSO-d_6	Eqm	NCH_2C, 3.25 (s); NCH_2N, 3.59 (s); CH, 5.62 (s)
15	Tri	Unsat; ^{2}D	−30	$CDCl_3$	VIII	NCH_2N, 3.90, 3.08 (ABq)
			−30	$CDCl_3$	IX	NCH_2N, 4.71, 3.44 (ABq)
			−30	$CDCl_3$	X	NCH_2N, 3.89, 3.81 (ABq); 3.81, 3.44 (ABq)
16	Tri	Sat	90	DMSO-d_6	Eqm	CCH_2C, 1.51 (s); NCH_2C, 2.40 (s); NCH_2N, 3.12 (s)
			−40	$CDCl_3$	VIII	CCH_2C, 1.65 (m); NCH_2C, 2.79, 2.37[p] (ABq); NCH_2N, 3.55, 3.05 (ABq)
17	Tri	Sat; ^{2}D	90	DMSO-d_6	Eqm	NCH_2N, 3.12 (s)
			−40	$CDCl_3$	VIII	NCH_2N, 3.55, 3.05 (ABq)

[a] Chemical shifts recorded in ppm downfield from Me_4Si. [b] See Table X for details. [c] Unresolved from overlap with other signals. [d] NCH_2C signals decoupled from CH_3. [e] Methyl region four peaks on decoupling from CH; see Figure 4. [f] May be interchanged with *j*. [g] Assignments made with reference to deuterated compounds. [h] May be interchanged with *k*. [i] May be interchanged with *l*. [j] See *f*. [k] See *h*. [l] See *i*. [m] Not possible to assign individually. [n] Spectrum unchanged at +30 °C. [o] Too much overlap at −30 °C; see ref 15. [p] On decoupling from adjacent CH_2 group.

work,[12] and concluded from the ^{1}H NMR spectrum (Table I) and vibrational spectra and dipole moment evidence that this compound exists as a mixture of set II (~80%) and set III (~20%). This conclusion is now completely confirmed by the ^{13}C NMR spectrum. At 25 °C, the ^{13}C NMR shows the expected three singlets (Table II); at −75 °C, the N-*C*-N splits into two singlets, clear evidence for the presence of two sets. In agreement the N-*C*-C and N-C-*C* peaks each split into *three* signals, of which we assign two of each three to set III (Figure 1, Scheme III).

The other peaks must be due to either set I or to set II, but the assignment to set II can be confirmed by comparison of the N-*C*-N chemical shifts with those of the unambiguously assigned (see later) corresponding peaks of the model compounds (**14** and **16**). There is no doubt that the peak at 58.6 ppm must be due to the set II conformation (Table III). At still lower temperatures, it should be possible to observe the slowing of the nonpassing nitrogen inversion barrier if the compound exists in set II rather than set I; in this case the set II substituent peak should split on further cooling. Unfortunately, the compound becomes so insoluble at these temperatures that it becomes difficult to distinguish between solute peaks and peaks due, presumably, to trace impurities in solute or solvent. Nevertheless there is some indication at −125 °C that the set II N-*C*-C peak *does* undergo further splitting, albeit with very small chemical shift difference: peaks are now observed at δ 49.3 and 48.9 ppm (Table II). This is, however, a much smaller chemical shift difference than is observed in the case of, for example, **14**, whose conformation X displays a $\Delta\delta$ of 7.9 ppm for the N-*C*-N carbon atoms. This may be due to the difference in structure, but the evidence here is not clear-cut, due largely to the difficulty of obtaining good spectra at the required temperatures.

From the ^{1}H NMR spectra, a barrier of 10.5 ± 0.2 kcal

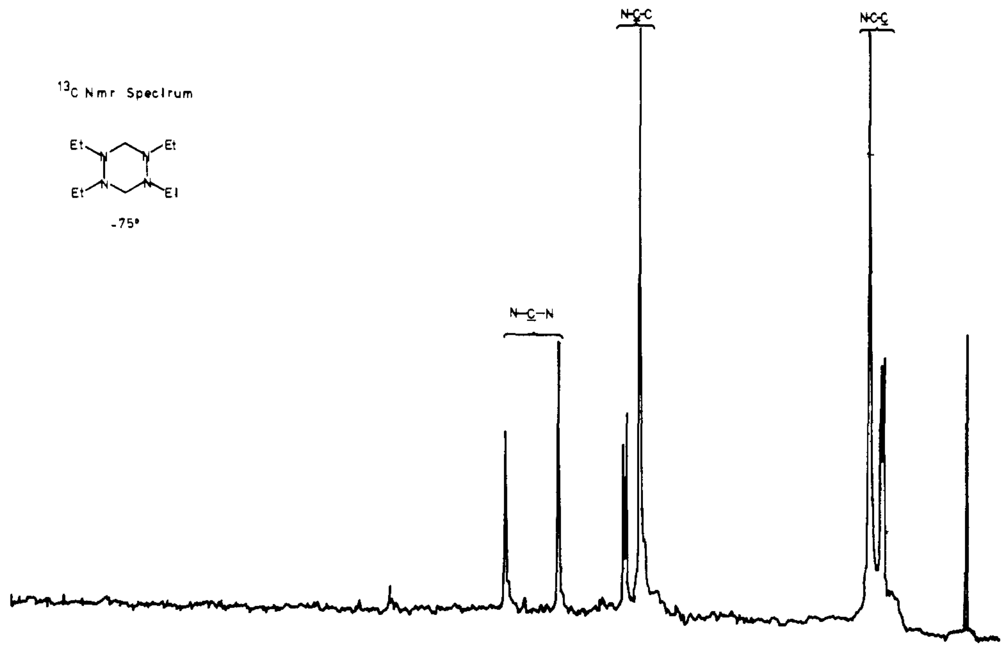


Figure 1. ^{13}C NMR spectrum of 1,2,4,5-tetraethylhexahydro-1,2,4,5- tetrazine at −75 °C in CF_2Cl_2.

Table II. ^{13}C NMR Data of Hexahydrotetrazines[a]

Compd No.	Ring	Substituent	Temp, °C	Solvent	Set	Peak assignment and chemical shift
1	Mono	Me_4	36	$CDCl_3 + CFCl_3$	Eqm	NC, 40.0; NCN, 70.6
			−90	$CDCl_3 + CFCl_3$	III	NC, 40.0, 40.8; NCN, 69.6
2	Mono	Et_4	25	CF_2Cl_2[b]	Eqm	NCC, 14.0; NCC, 48.2; NCN, 61.8
			−75	CF_2Cl_2	II	NCC, 14.3; NCC, 47.1; NCN, 58.6
			−75	CF_2Cl_2	III	NCC, 13.7, 13.5; NCC, 49.2, 49.6; NCN, 66.4
			−125	CF_2Cl_2	II	NCC, 14.9; NCC, 48.9, 49.3;[c] NCN, 59.5
			36	CDCl + $CFCl_3$	Eqm	NCC, 20.5; NCC, 49.8; NCN, 55.6
3	Mono	i-Pr_4	−140	CF_2Cl_2	I	NCC, 21.8, 22.0; NCC, 52.7; NCN, 79.6
			−140	CF_2Cl_2	III	NCC, (20.5, 20.8), (22.6, 22.9); NCC, 46.1, 47.4; NCN, 67.9
4	Mono	Bz_4	36	$CDCl_3$	Eqm	NCC, 54.6; NCN, 62.8; Ar, 127.1, 128.2, 129.3
			−70	CH_2Cl_2[b]	II	NCC, 51.4; NCN, 60.9; Ar, 127.3, 128.4, 129.8
5	Mono	Me_2Bz_2; sym	36	$CDCl_3 + CFCl_3$	Eqm	NC, 39.5; NCC, 56.1; NCN, 67.5; Ar, 127.4, 128.6, 129.1
			−90	$CDCl_3 + CFCl_3$	II	NC, 33.7; NCC, 52.0, NCN, 63.6; Ar, 137.0, 137.8, 138.4
			−90	$CDCl_3 + CFCl_3$	III	NC, 40.7; NCC, 55.6, 56.6; NCN, 67.8, 68.7; Ar, 127.0, 128.3
14	Tri	Unsat	90	DMSO-d_6[b]	Eqm	NCC, 47.9; NCN, 71.2; NCC, 122.9
			−30	CH_2Cl_2	IX, X	NCC, vicinal trans lone pair, 40.0, 40.8
			−30	CH_2Cl_2	VIII, IX, X	NCC, vicinal gauche lone pair, 50.0, 50.7, 51.2, 51.9, 52.4
			−30	CH_2Cl_2	IX	NCN, 65.3
			−30	CH_2Cl_2	X	NCN, 68.3, 76.2
			−30	CH_2Cl_2	VIII	NCN, 80.0
			−30	CH_2Cl_2	VIII, IX, X	NCC, 122.5, 122.8, 123.0, 123.5, 124.0
16	Tri	Sat	90	DMSO-d_6	Eqm	NCC, 24.1; NCC, 52.9; NCN, 80.1
			−30	$CDCl_3 + CFCl_3$	VIII	NCC, 23.8; NCC, 52.5; NCN, 79.7

[a] Spectra recorded as ppm downfield from Me_4Si. [b] 0.5 ml acetone-d_6 added for internal deuterium lock with these solvents. [c] Spectral region somewhat confused.

mol^{-1} was determined; this is assigned as a passing N-methyl inversion barrier. Because of the poor quality of the very low temperature spectra only a rough estimate of the nonpassing barrier could be made: 7.1 ± 1.0 kcal mol^{-1}.

^{13}C Chemical Shifts. We find that the ^{13}C chemical shifts of the N-*C*-N carbon atoms in hexahydrotetrazines offer a convenient criterion for differentiation between set I and set II. By using the tricyclic hexahydrotetrazines **14** and **16** as models (cf. later discussion), it is evident that the shift for set I is considerably higher than that for set III which is again higher than for set II. Assignments can thus readily be made for the monocyclic hexahydrotetrazines (Table III).

1,2,4,5-Tetrapropylhexahydro-s-tetrazine (3). We have not previously studied this compound. Nelsen et al.[7] have reported its behavior on electron cyclic voltammetry, but no work on its conformation has been published. In the ^{13}C NMR spectrum (Table II) the expected three singlets at 36 °C coalesce on lowering the temperature, and at −140 °C (Figure 2) the N-*C*-N peak shows as *two* singlets pointing to a mixture of two sets. The methine carbon peak, in agreement, shows a larger singlet at δ 52.7 which could belong to set I or II and a smaller doublet at δ 46.1 and 47.4 assigned to set III. The methyl carbon atoms are diastereotopic in sets I, II, and III; additionally in set III there are two types of isopropyl group. The intense doublet and two weaker doublets (Figure 2, Table II) confirm the presence of set III with either set I or set II. The marked difference in intensity of the two weak doublets for N-C-*C* is ascribed to differential NOE. The predominant conformation is shown to be set I rather than II by the high value for the chemical shift of N-*C*-N in comparison with

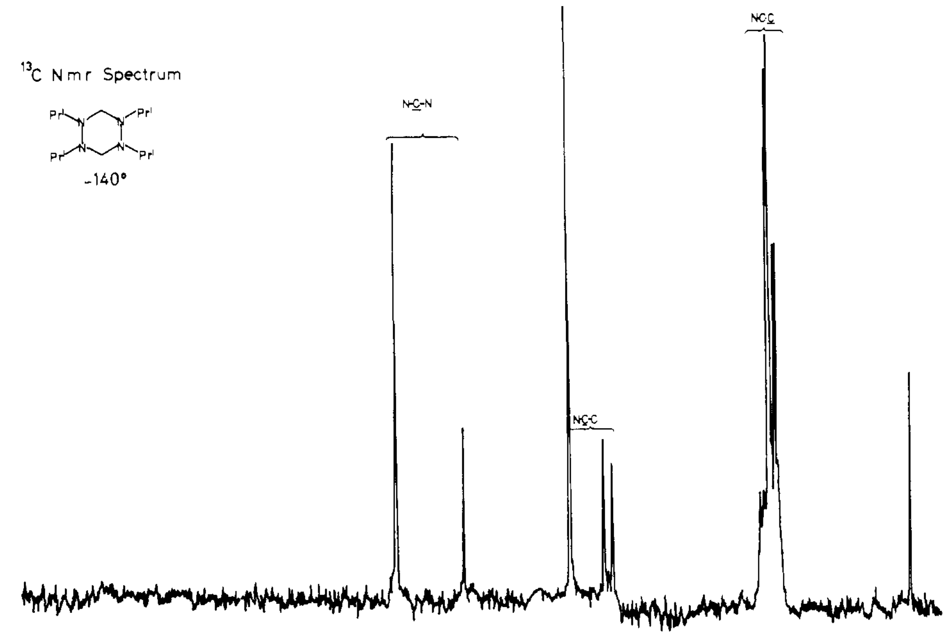


Figure 2. ^{13}C NMR spectrum of hexahydro-1,2,4,5-tetraisopropyl-1,2,4,5-tetrazine at −140 °C in CF_2Cl_2.

Table III. ^{13}C Chemical Shifts of N–C–N Carbon Atoms[a] in Hexahydrotetrazines[b]

Compd					
No.	Ring	Substituent	Set I, VIII	Set III, X	Set II, IX
1	Mono	Me_4		69.6[c]	
2	Mono	Et_4		66.4	58.6
3	Mono	i-Pr_4	79.6	67.9	
4	Mono	Bz_4			60.9
5	Mono	Me_2Bz_2; sym		68.7, 67.8	63.6
14[c]	Tri	Unsat	80.0	76.2, 68.3	65.3
16	Tri	Sat	79.7		

[a] Ppm downfield from Me_4Si. [b] Recorded at temperatures where passing nitrogen inversion is slow on the NMR time scale. [c] Previously assigned from ^1H NMR data.

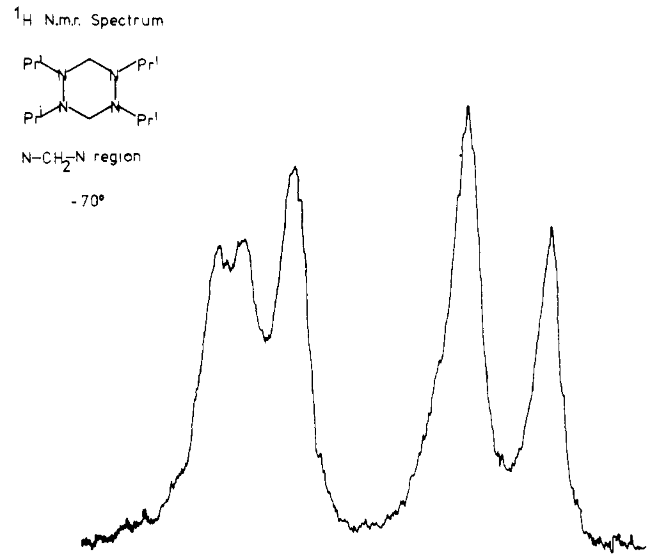


Figure 3. N-CH_2-N region of the ^1H NMR spectrum of hexahydro-1,2,4,5-tetraisopropyl-1,2,4,5-tetrazine at −70 °C in CF_2Cl_2.

those of the unambiguously assigned model compounds **14** and **16** (Table III).

Interpretation of the low temperature proton NMR spectra is less simple in this case and relies on the ^{13}C NMR conclusions. The N-CH_2-N peaks can be regarded as two AB quartets almost superposed (Figure 3). The CH peak is diffuse; the CH_3 pattern at 220 MHz when decoupled from the CH we interpret as the near superposition of three doublets as indicated (Figure 4). If this interpretation is correct, the two sets I and III are approximately equally populated in the tetraisopropyl compound, which is in fair agreement with the conclusion from the ^{13}C NMR spectrum. The passing N-inversion barrier was found to be 10.3 kcal mol^{-1}, similar to that for the tetraethyl but somewhat lower than that for the tetramethyl compound.

The vibrational spectra are too poorly resolved to be of value but the low dipole moment of 1.19 D (cyclohexane) is consistent with a preponderance of a centrosymmetric set.

1,2,4,5-Tetrabenzylhexahydro-*s*-tetrazine (4). This compound has not previously been examined. In the ^1H spectrum, coalescence occurs at −29 °C to give a single AB quartet for ring CH_2 and one for the $PhCH_2$: the lower field half of the AB quartet from the ring CH_2 and the lower field half of the AB quartet of the benzyl CH_2 overlap almost exactly, as is shown by decoupling experiments (Figure 5). This indicates the occurrence of a single set I or II. The passing N-inversion barrier was determined as 11.5 ± 0.2 kcal mol^{-1}.

The ^{13}C NMR spectrum showed little change down to −100 °C although at the lowest temperatures the N-C peaks are broadened, probably indicating proximity to a coalescence temperature. Unfortunately, studies at still lower temperatures were unsuccessful because the compound crystallized out of vinyl chloride, CCl_2F_2, and CF_3Br. The ^{13}C chemical shifts for N-C-N (Table III) clearly point to set II rather than set I for this compound.

Although the ^{13}C NMR data at −70 °C (Table II) studied in CH_2Cl_2 and the ^1H NMR data at −80 °C (Table I) studied in CF_2Cl_2 seem unequivocally to point to a centrosymmetric set (I or II), the observed dipole moment, 1.74 D (Table IV) (in cyclohexane), is very high for a centrosymmetric molecule. Further the vibrational spectral comparison (Table V), which indicates 34 coincidences out of 40 possible, favors the noncentrosymmetric set III.

It appeared that the different conclusions from the various methods might be due to difference in the position of the conformational equilibrium caused either by temperature or sol-

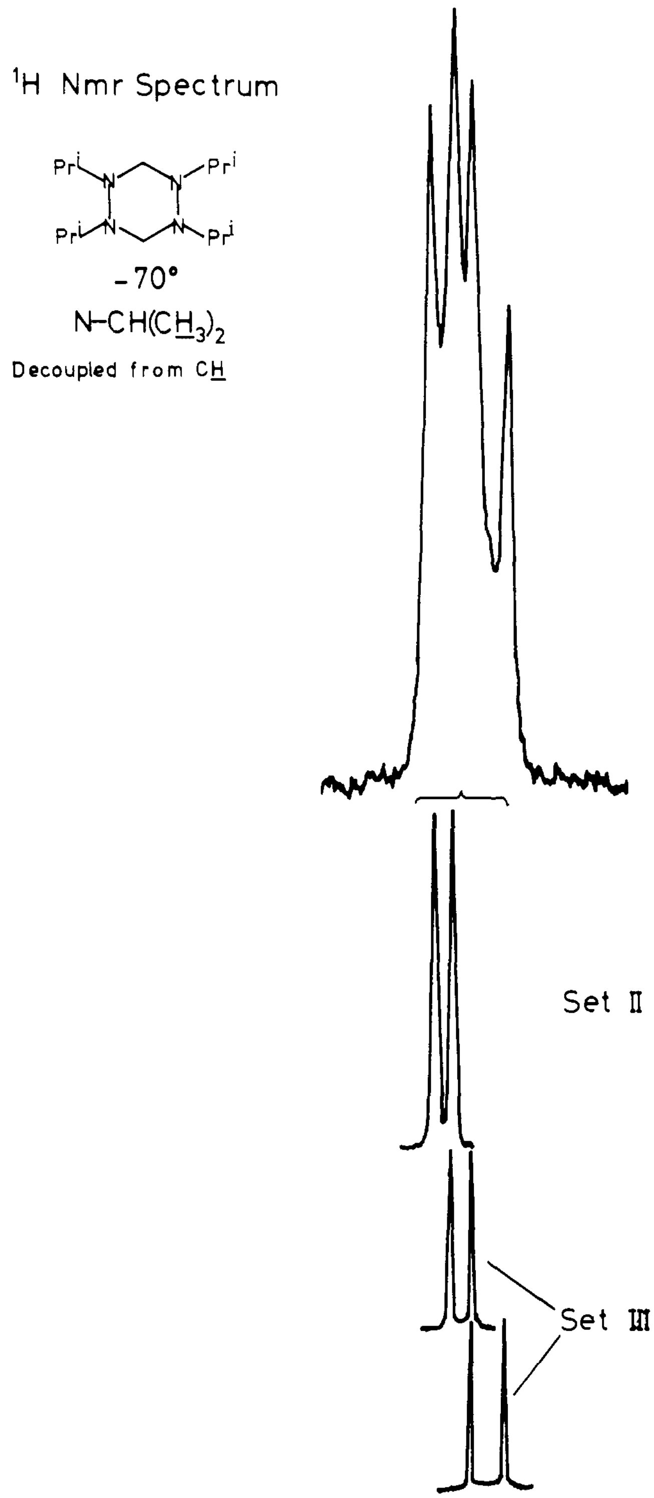


Figure 4. Isopropylmethyl region of the ^{1}H NMR spectrum of hexahydro-1,2,4,5-tetraisopropyl-1,2,4,5-tetrazine at −70 °C in CF_2Cl_2, decoupled from the methine proton.

vent. The solvent and temperature dependence in the ^{1}H NMR spectra of compound **4** have been investigated (Table VI; unfortunately it was difficult to obtain spectra below the coalescence point, because of solubility difficulties). The variations are not large and no clear pattern emerges. We believe that, at least in the above solvents, set II predominates. An x-ray investigation of this compound is in hand.

1,4-Dibenzylhexahydro-2,5-dimethyl-*s*-tetrazine (5). The room temperature ^{13}C spectrum shows the expected six peaks (Table II) each of which splits at −90 °C to give peaks assigned as in Figure 6. This is clearly consistent with a mixture of set

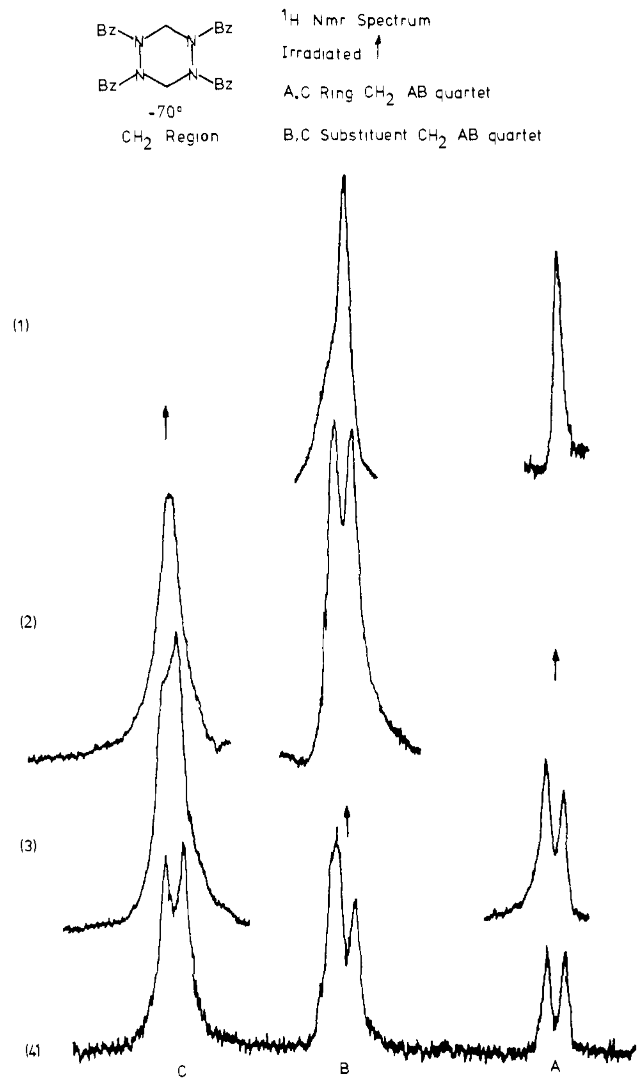


Figure 5. ^{1}H NMR spectrum of 1,2,4,5-tetrabenzylhexahydro-1,2,4,5-tetrazine at −80 °C in $CDCl_3$–$CFCl_3$.

III (the major component) together with *either* set I or set II; evidently the expected two CH_3 peaks for set III are superposed. The N–*C*–N ^{13}C chemical shifts (Table III) show that it is set II rather than set I which is the symmetric set coexisting with set III.

While the ^{1}H NMR spectrum of **5** at 34 °C is simple (Table I), that at −80 °C is very complex in the CH_2 region (Figure 7, Table I); it was assigned using the selectively deuterated compound **6** spectrum (Figure 8). Six overlapping CH_2 AB quartets are found, in good agreement with set III mixed with *either* set I *or* set II; the methyl region of the spectrum at −80 °C, showing three peaks, confirms these conclusions. Integration of the peaks indicates about 65% of the unsymmetric set III and 35% of the symmetric set; this results in AB quartets which are of equal size, since two AB quartets are found in set III for one in sets I or II. The barrier to the passing N inversion was determined as 12.1 ± 1.0 kcal mol^{-1}.

Vibrational spectroscopy indicates a substantial proportion of noncentrosymmetric conformation: of 12 Raman bands, 7 show coincidence (Table V). The dipole moment (Table IV) of 1.40 D (in benzene) is at the intermediate level, as expected for a mixture of conformations.

2,4-Dibenzylhexahydro-1,5-dimethyl-*s*-tetrazine (7). The ^{1}H NMR spectrum is again complex and again the deuterated compound **8** was used to facilitate interpretation. Results are similar to those of its isomer **5**; the six expected AB quartets

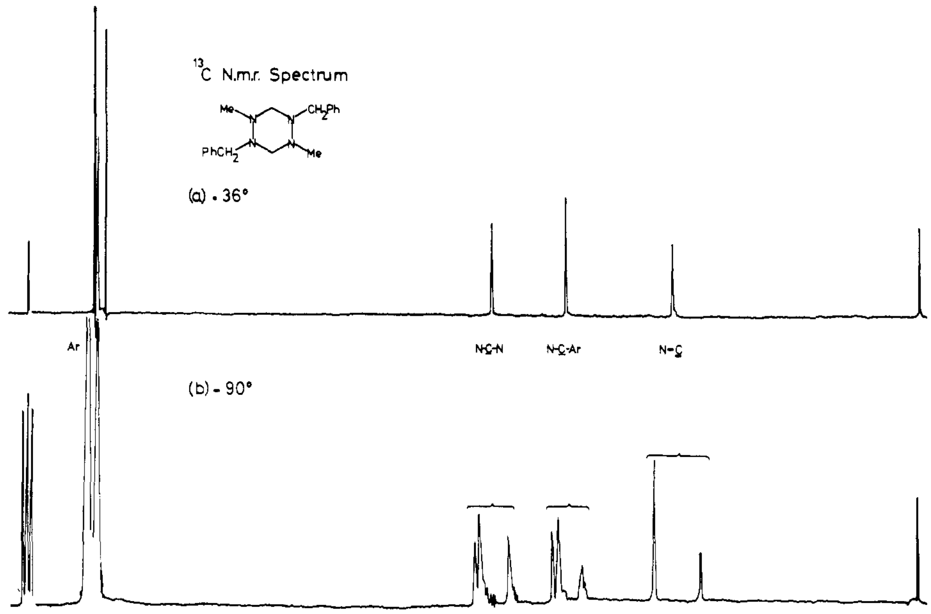


Figure 6. ^{13}C NMR spectrum of 2,5-dibenzylhexahydro-1,4-dimethyl-1,2,4,5-tetrazine at −90 °C in $CDCl_3$-$CFCl_3$.

Table IV. Dielectric and Specific Volume Measurements and Dipole Moments at 25 °C

(a) Dielectric and Specific Volume Measurements[a]

Compd No.	Ring	Subst	ω	$(\epsilon_{12} - \epsilon_1)$	$(\nu_1 - \nu_{12})$	Solvent
1[b]	Mono	Me_4	536	884	114	Cyclohexane
			2524	3423	553	
			4212	5426	894	
			5497	7565	1213	
2[b]	Mono	Et_4	2210	1125	415	Cyclohexane
			4184	2183	769	
			5667	2931	1040	
			7763	4006	1420	
3	Mono	i-Pr_4	1108	618	184	Cyclohexane
			1270	709	197	
			2009	1137	361	
			4193	2363	732	
			5803	3260	988	
4	Mono	Bz_4	1605	1013	382	Benzene
			2491	1517	583	
			4424	2596	1060	
			6872	4040	1702	
5	Mono	Me_2Bz_2 sym	1778	1556	352	Benzene
			3045	2684	602	
			4975	4183	970	
			7903	6693	1608	
16[c]	Tri	Sat	3334	1755	1003	Cyclohexane
			3512	1855	1047	
			4052	2144	1202	
			5591	2894	1666	

(b) Dipole Moments

No.	$d\epsilon/d\omega$	$-d\nu/d\omega$	$T^P{}_{2\infty}$	E^P	μ/D
1	1.340 ± 0.04	0.219 ± 0.004	85.55	41.82	1.46 ± 0.02
2	0.517 ± 0.003	0.183 ± 0.001	81.03	59.99	1.01 ± 0.01
3	0.563 ± 0.002	0.173 ± 0.004	107.20	78.16	1.19 ± 0.01
4	0.574 ± 0.005	0.251 ± 0.004	167.86	106.28	1.74 ± 0.01
5	0.833 ± 0.002	0.204 ± 0.005	129.49	89.33	1.40 ± 0.02
16	0.502 ± 0.009	0.296 ± 0.004	73.15	55.78	0.92 ± 0.02

[a] ω = Weight fraction of solute; ϵ = dielectric constant; ν = specific volume; suffixes 1 and 12 refer to solvent and solution, respectively; all values are multiplied by 10^6. [b] Reference 2. [c] R. Scattergood, unpublished results.

are somewhat difficult to distinguish because of overlap, but the evidence points to a mixture of sets III and either II or I. Insufficient compound was available for ^{13}C NMR investigation.

1,4-Dibenzylhexahydro-2,5-diisopropyl-*s*-tetrazine (9). The 34 °C ^1H NMR spectrum (Table I) coalesces on temperature lowering and shows at −80 °C four equal doublets in the CH_3 region: the double pattern is due to coupling; the isopropyl methyl groups are also diastereotopic, hence there are just *two* types of isopropyl group. That these probably arise from set III is confirmed by the CH_2 region which shows four overlapping AB quartets (Table I). Two of these are from the ring methylene protons and two from the benzyl methylene groups, and all are, as expected, of equal size. This pattern could however also arise for equal amounts of sets I and II. Insufficient compound was available for ^{13}C examination.

Bicyclic Hexahydro-*s*-tetrazines (10–13). We consider the bicyclic hexahydro-*s*-tetrazines together. The room temperature ^1H NMR spectral assignments are collected in Table I and show no unusual features. At low temperatures, a single AB pattern for the N-CH_2-N group and a single N-alkyl environment is found for each of the four compounds (Table I). This behavior is consistent with existence of each of **10–13** in a single set, which must be either set IV or set VII (Scheme III).

6*H*,13*H*-1,4,8,11-Tetrahydrobis(pyridazino[1,2-*a*; 1′,2′-*d*]-*s*-tetrazine) (14). The assignment of the ^1H NMR spectrum for this compound and the deuterated analogue **15** has previously been discussed in detail.[2] The ^{13}C NMR spectrum (Figure 9) offers striking confirmation of these conclusions. At +90 °C three singlets are observed for N-*C*-N, N-*C*-C, and vinyl-C. At −30 °C, the N-*C*-N splits into four peaks (one for VIII, one for IX, and two for X), the N-*C*-C into seven peaks (one for VIII, two for IX, and four for X); and the vinyl-C into six peaks [one for VIII, two for IX, three for X (four are expected but two evidently coincide)].

As mentioned above, the proton spectra for this compound have been unequivocally assigned.[2] The ^{13}C spectra can then be in turn unequivocally assigned in the N-*C*-N region provided the peak sizes are proportional to the conformer amounts. Differential NOE means this is not normally true, but a suppressed Overhauser gated decoupling program[19] canceled the NOE and enabled the assignment of the N-*C*-N peaks as given in Table II. Variation of ^{13}C chemical shift of this compound with solvent has been checked (Table VII) and found to be very small indeed.

The passing N-inversion barrier in this compound is also simultaneous with ring inversion of the terminal ring and as

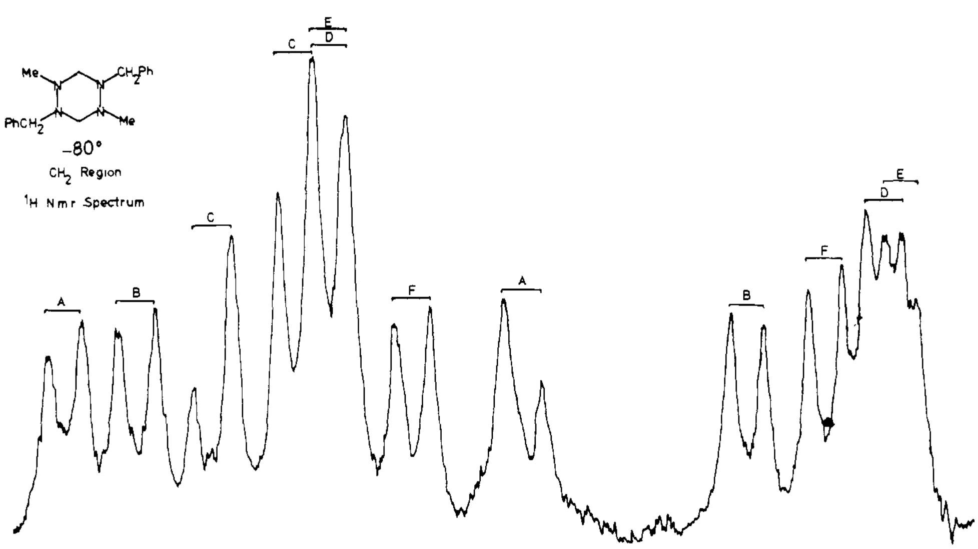
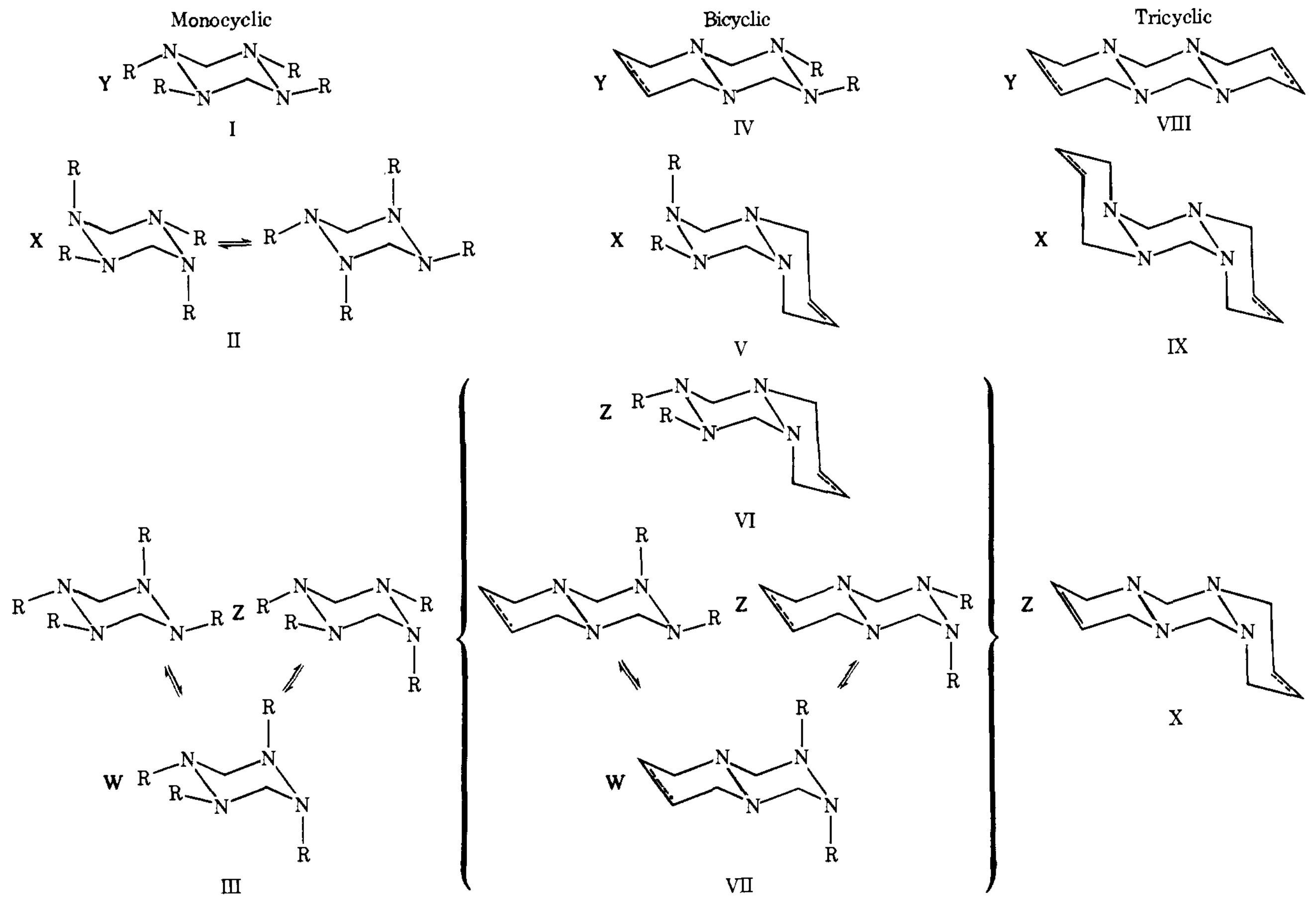


Figure 7. Methylene region of the ^1H NMR spectrum of **5** at −80 °C in $CDCl_3$-$CFCl_3$.

Scheme III. Conformational Sets and Types of Hexahydro-*s*-tetrazines



expected is higher (14.2 ± 0.2 kcal mol^{-1}) than for the other compounds.

6*H*,13*H*-Octahydrobis(pyridazino[1,2-*a*;1′,2′-*d*]-s-tetrazine) (16). We concluded[2] from the ^1H NMR that this compound exists exclusively in set VIII. The ^{13}C NMR spectrum (Table II) is essentially invaiant with temperature over the range +30 to −60 °C and the existence of the three peaks confirms set VIII. To confirm conclusively the assignment of the central ring methylene AB quartets, we have obtained the ^1H spectrum of the deuterated compound **15** at low temperature (−30 °C) (see Table I). The dipole moment of this compound was previously found to be 0.92 D in cyclohexane;[20] this, although a relatively low value, is still surprisingly high for a symmetric molecule, with all trans diaxial lone pairs on the nitrogen atoms.

Comparison of models for the bisolefinic compound **14** and the saturated analogue **16** suggest that cis fusion of rings in **16** will be considerably less favored than in **14** as a consequence of cross-ring interactions. The exclusive existence of **16** in the single set VIII is in good agreement with this reasoning. The passing N-inversion barrier (from the ^1H NMR spectrum) is 18.4 kcal mol^{-1}.

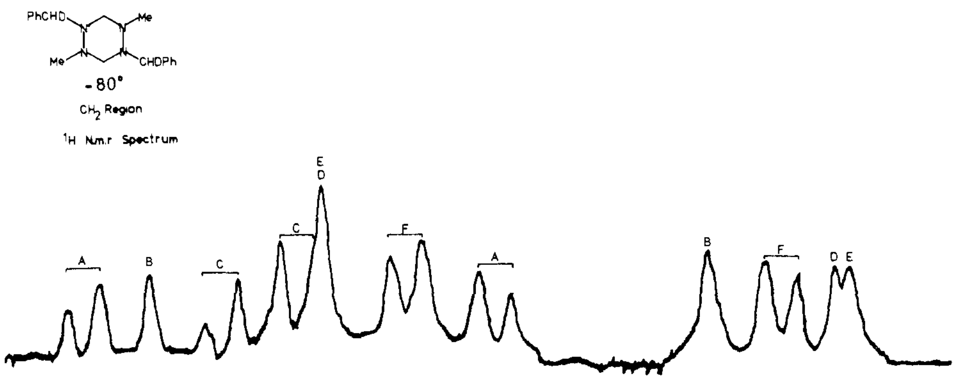


Figure 8. Methylene region of the [1]H NMR spectrum of **6** at −80 °C in $CDCl_3$-$CFCl_3$.

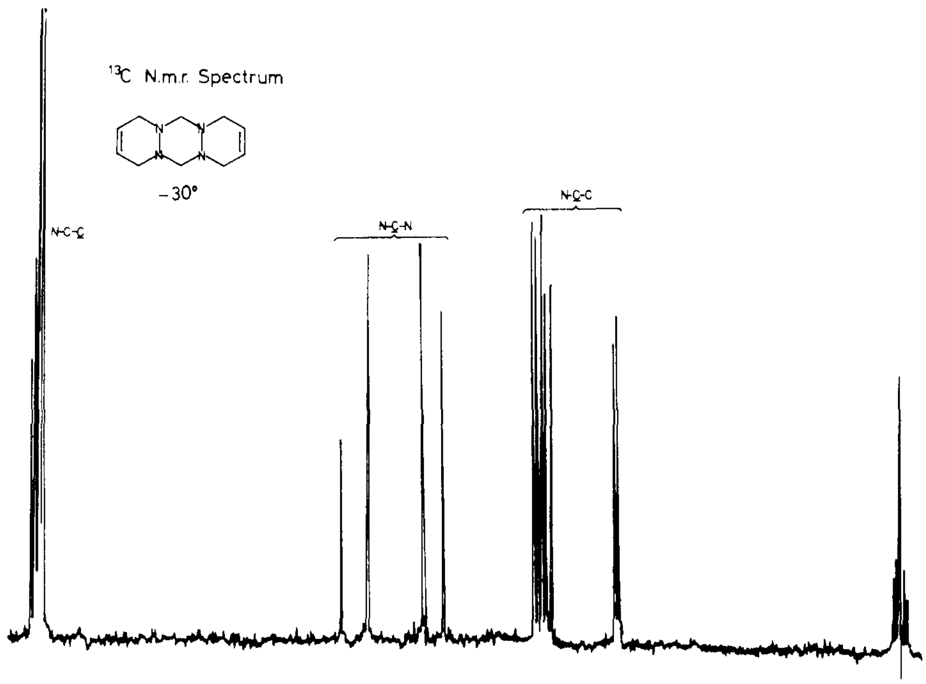


Figure 9. [13]C NMR spectra of **14** at: −30 °C in CH_2Cl_2.

Rationalization of Conformational Equilibria of Tetrazanes

Tricyclic Tetrazanes (Table IX). Entropy differences exist between conformations VIII, IX, and X[21] (each set here consists of a single conformation as detailed in Scheme III). Assuming that the only entropy terms arise from symmetry numbers and from *dl* pairs, the ΔH difference between the conformations for the bisolefinic compound **14** is (see Table VIII) as follows:

$$\Delta H_{\mathrm{VIII},245} \rightarrow \Delta H_{\mathrm{IX},245} = +120 \text{ cal}$$

$$\Delta H_{\mathrm{VIII},245} \rightarrow \Delta H_{\mathrm{X},245} = +220 \text{ cal}$$

If the two ends of the molecule act independently of each other, we would expect ΔH for VIII → IX to be twice ΔH for VIII → X, and the figures agree with this very well, which is further confirmation of the correctness of the original assignments and the validity of the method.

Bicyclic Hexahydro-*s*-tetrazines (Table IX). The spectral evidence shows conclusively that the compounds **10–13** exist exclusively in either set IV *or* set VII. For the unsaturated derivatives, the above reasoning for the tricyclic analogue suggests that the ΔH difference between set IV and set VI must be very small. This indicates then that it is set VII which is populated. Further, within set VII, conformation W is expected to dominate as a low ΔH difference is expected between conformation Z and set V.

This conclusion is at variance with the Δ_{AB} proton chemical shift difference criterion, previously suggested.[2] However, a detailed consideration of such Δ_{AB} chemical shift increments (Table X) shows that there is no clear correlation between Δ_{AB} and conformation: set I 0.2–0.8, set II 0.6–1.7, set III 0.1–0.7. Usually the set II values are higher than the other sets, but overlap occurs. We now believe that Δ_{AB} is not a reliable criterion of conformation in the present series. Equally, the J_{gem} criterion does not offer any hope of even a qualitative interpretation and these conclusions apply to the C-CH_2-N as well as N-CH_2-N groups. These conclusions are similar to those reached earlier for other series of saturated heterocycles.[22]

Conformer Population within Set III. We have already adduced evidence for the predominance of conformation W within set III (or set VII for the bicycles): the lack of a second coalescence for the simple tetramethyl **1** and tetraethyl **2** compounds; a thermodynamic argument for the bicyclic compounds **10–13**; and a steric effect for the tetraisopropyl compound **3**. An additional gauche butane interaction is observed in conformation Z compared with conformation W in compound **3**. The [13]C chemical shifts for the N-*C*-C collected in Table XI suggest that conformation W predominates in *all* cases. For compound **14** the two axial N-*C*-C resonances are ca. 10 ppm to higher field than those of their five *equatorial* analogues. However, this cannot be a general consequence of

Table V. Comparison of Ir Frequencies and Raman Displacements for Some Hexahydrotetrazines[a]

Ir	Raman	Ir	Raman	Ir	Raman
		Tetrabenzyl (**4**)			
1601	1601	1151	1151	830	825
1586	1584	1125	1121	806	
1574	1570	1107	1102	794	794
1492		1077	1073	775	
1461	1460	1061		763	
1451		1047			750
1447	1446	1026	1026	736	733
1443		1002	1002	707	705
1373	1368		991	697	700
1354		979		632	635
1344	1347	969		624	621
1340	1339	959	955	619	615
1303	1301		942	584	
1286	1287	915	913		565
1235	1234	886			533
1208	1206		875	510	514
1199		844		485	481
1171	1171	837	836	467	471
		Dimethyldibenzyl (5)			
1608	1605	1366	1370		1158
1587	1585		1216		1033
1454	1451	1201	1198		1005
1413	1410		1178		959

[a] For data on compounds 1 and **2**, see ref 2.

Table VI. Variation of ^1H Chemical Shift of Tetrabenzylhexahydro-*s*-tetrazine with Solvent and Temperature

Solvent	Temp, °C	Chemical shift[a]
CH_2Cl_2	90	3.72
$CDCl_3$	90	3.77
CCl_4	90	3.63
Cyclohexane	90	3.69
$CDCl_3 + CFCl_3$	32	3.77
$CDCl_3 + CFCl_3$	−25	3.75
$CDCl_3 + CFCl_3$	0	3.75
$CDCl_3 + CFCl_3$	−25	3.74
$CDCl_3 + CFCl_3$	−50[b]	3.75
$CDCl_3 + CFCl_3$	−75	3.70[c]
$CDCl_3 + CFCl_3$	−90	3.69[c]

[a] Chemical shift of ring methylene protons recorded ppm downfield from Me_4Si. [b] Near coalescence temperature. [c] Midpoint of AB quartet.

Table VII. Variation of ^{13}C NMR Chemical Shifts of Compound **14** with Solvent

Solvent	Temp, °C	Chemical shifts of N–C–N carbon atoms[a]
$CDCl_3 + CFCl_3$	−40	80.0, 76.1, 68.1, 65.3
CH_2Cl_2[b]	−40	80.0, 76.2, 68.3, 65.3
CCl_4	−40	80.0, 76.1, 68.2, 65.3
DMSO-d_6	+90	71.2[c]

[a] Chemical shift in ppm downfield from Me_4Si. [b] Acetone-d_6 added for internal lock. [c] Above coalescence temperature.

Table IX. Conformer Populations (%) of Hexahydrotetrazines

Compd			Set		
No.	Ring	Substituent	I, IV, VIII	II, V, IX	III, VI, VII, X
1	Mono	Me_4			100
2	Mono	Et_4		80	20
3	Mono	*i*-Pr_4	50,[a] 60[b]		50, 40
4	Mono	Bz_4		100	
5	Mono	Me_2Bz_2; sym		35	65
7	Mono	Me_2Bz_2; unsym		35	65
9	Mono	*i*-Pr_2Bz_2; sym			100[c]
10	Bi	Me_2; unsat			100
11	Bi	Et_2; unsat			100
12	Bi	*i*-Pr_2; unsat			100
13	Bi	Me_2; sat			100
14	Tri	Unsat	13	20	66
16	Tri	Sat	100		

[a] ^1H NMR results. [b] ^{13}C NMR results. [c] May be 50% set I, 50% set II; see text.

the axial or equatorial conformation because if this were the case the difference in the chemical shifts between the two types of N–C–C in set III should be at least 5 ppm for conformation Z (ae ⇌ ea R groups time averaged to 50% axial) up to 10 ppm for conformation W. We believe that the shift to higher field is due to a vicinal anti lone pair for the axial CH_2 groups in sets IX and X. Some evidence for the existence of this effect is available from model compounds[23] **20** and **21.**

Thus, in the cycloalkane, $\Delta\delta_{ab}$ is 7.23 ppm; in the hydrazine $\Delta\delta_{ab}$ is 9.4 ppm. As the differences in chemical shift for the two types of N–*C*–C carbon atoms of set III are small (0.0–1.6 ppm) we believe that conformation Z is much less populated than conformation W in all cases because W does not have an anti lone pair vicinal to an axial R, while Z does. Comparison of the shifts for sets I and II supports this view: Set I contains only equatorial groups and at least for **3** and **16** occurs at rather low field. Set II shows shifts for rapidly equilibrating 50% equatorial:50% axial groups; if the equatorial shifts are at lower field then the axial groups must be at higher field; these axial groups possess vicinal anti lone pairs and should indeed come at higher field. The whole pattern is consistent.

Nelsen and Weisman[24] observed the axial N-methyl group ^{13}C NMR shift at high field and explained it as due to steric crowding; we believe that at least part of the effect is caused by the vicinal anti lone pair as explained above.

Rationalization of Conformational Populations of Hexahydro-*s*-tetrazines. If entropy considerations dominated, then conformations Y:Z:X:W would coexist in the ratio 1:8:2:4 (see Table XII). We have seen that W/Z is always large (except for the tricyclic compounds where W cannot exist); this must be due to a ΔH term caused by electronic as well as steric reasons: electronically a 1,3-diaxial lone pair to lone pair interaction present in Z is rlieved in W, and sterically the ae conformation of Z is less favored than the aa of W. An electronic term α, similar to that just discussed, will favor X over Z and Z in turn over Y. However, an important steric term β can favor Y over Z, and in turn Z over X. The relative sta-

Table VIII. Energy Parameters for Compound 14

Set	Symmetry no.[a]	Entropy term from Symmetry no.	Entropy term from *dl* pair	Total entropy term	K[b]	$T\Delta S_{245}$[c]	$\Delta G = -RT \ln K$[c]	ΔH[c]
VIII	4	$-R \ln 4$	0	−2.76	1	0	0	0
IX	2	$-R \ln 2$	0	−1.38	1.54	0.33	−0.21	0.12
X	1	0	$+R \ln 2$	+1.38	5.08	0.99	−0.77	0.22

[a] Reference 21. [b] Reference 2. [c] Relative to VIII.

Table X. ¹H NMR Chemical Shifts and Coupling Constants of AB Quartets

Compd			N–CH₂–N						N–CH₂–C					
			Δ_{AB}, ppm			J_{gem}, Hz			Δ_{AB}, ppm			J_{gem}, Hz		
No.	Ring	Substituent	Set I	Set II	Set III[a]	Set I	Set II	Set III	Set I	Set II	Set III	Set I	Set II	Set III
1	Mono	Me_4			0.64			12.0						
2	Mono	Et_4		1.7[b]	0.31		14.0	12.0		0.4[b,c]	0.3, 0.7		12.0	7.0, 7.0
3	Mono	i-Pr_4	0.2[b]		0.2[b]	12.5		12.5						
4	Mono	Bz_4		1.16			12.0			0.48			11.0	
5[d]	Mono	Me_2Bz_2; sym		0.75	0.67, 0.12		12.0	12.0, 13.0		1.01	0.93, 0.90		13.0	9.0, 11.0
7[e]	Mono	Me_2Bz_2; unsym		0.57	0.39, 0.29		14.0	12.0, 12.0		*f*			*f*	
9	Mono	i-Pr_2Bz_2; sym			0.16, 0.04			12.0, 12.8			0.21, 0.10[g]			5.0, 5.0
10	Bi	Me_2; unsat			0.57			12.5						
11	Bi	Et_2; unsat			0.19			14.5						
12	Bi	i-Pr_2; unsat			0.03			4.0						
13	Bi	Me_2; sat			0.19			14.5						
14	Tri	Unsat	0.82	1.54	0.08, 0.37	9.5	11.5	11.5, 9.5						
16	Tri	Sat	0.50			9.5			0.42			12.0		

[a] Sets denoted as for monocycles; corresponding sets for bicycles respectively IV, V, and VI or VII; for tricycles VIII, IX, and X. [b] Partially obscured. [c] On decoupling from CH_3. [d] Assignments made with reference to 6; some may be interchanged. [e] Assignments made with reference to 8; some may be interchanged. [f] Unresolved region 4.0–4.3; 3.67 ppm. [g] Assignments based on coupling constant of **4**.

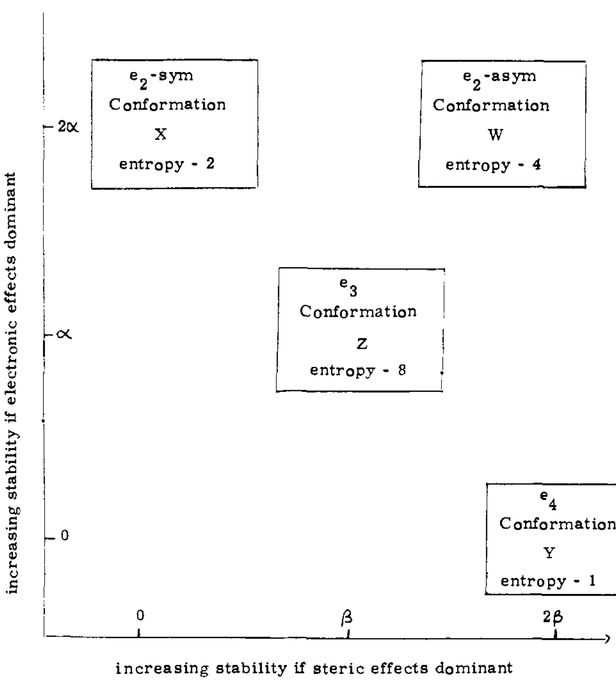
Table XI. ¹³C NMR Chemical Shifts of Substituent α-Carbon Atoms in Hexahydrotetrazines

Compd					
No.	Ring	Substituent	Peak	Set	Chemical shift[a]
1	Mono	Me_4	N–CH_3	III	40.0, 40.8
2	Mono	Et_4	N–CH_2–CH_3	II	47.1
				III	49.2, 49.6
3	Mono	i-Pr_4	N–$CH(CH_3)_2$	I	52.7
				III	46.1, 47.4
4	Mono	Bz_4	N–CH_2–Ph	II	51.4
5	Mono	Me_2Bz_2; sym	N–CH_2–Ph	II	52.0
				III	55.6, 56.6
			N–CH_3	II	33.0
				III	40.7
14	Tri	Unsat	N–CH_2–C	IX, X[b]	40.4, 40.8
				VIII, IX, X[c]	50.0, 50.7, 51.2, 51.9, 52.4
16	Tri	Sat	N–CH_2–C	VIII	52.5

[a] Chemical shifts recorded as ppm downfield from Me_4Si. [b] Vicinal trans lone pair. [c] Vicinal gauche lone pair.

bilities of the four conformations are represented in Scheme IV, and this enables the clarification and rationalization of the main features of the conformational equilibria in this series as follows:

Scheme IV. Relative Stabilities of Conformations



(i) For the unsaturated tricyclic compound **14**, the terms α and β approximately cancel; W cannot exist but the other three conformations X, Z, and Y, are all significantly populated.

(ii) For the saturated tricyclic compound **13**, the steric term is dominant and the net ΔH term favors Y with Z unimportant and X very small indeed (Table IX).

(iii) For the tetraisopropyl derivative **3**, the steric term is again dominant; indeed models show that severe interactions will prevent two adjacent isopropyl groups in the ae conformations. Hence compound **3** exists in sets I and III, and within set III, conformation W alone is significantly populated. Intermediate dipole moment value (Table IV) (1.18 D) and Raman/ir symmetry evidence (Table V) (7 coincidences/12) are in agreement with this mixture of symmetric and noncentrosymmetric sets.

(iv) The fact that **3** exists appreciably in conformation Y as well as in W whereas the bicyclic analogue **12** exists only in set VII and not in set IV must be due to secondary influences: two adjacent equatorial N-isopropyl groups probably cause somewhat more crowding in the axial positions opposite because of butressing than occurs for a fused ring; the $(CH_2)_4$ chain in the bicyclic compounds prefers the diequatorial conformation for steric reasons, and the other groups then take up the diaxial positions to give conformation W in each case.

(v) The monocyclic tetrazines investigated, apart from the tetraisopropyl derivative, all exist in conformations X and/or

Table XII. Entropy Factors for Individual Conformers

Conformer	Symmetry no. factor[a]	*dl* pair factor	Total symmetry factor
Y	1	1	1
Z	4	2	8
X	2	1	2
W	2	2	4

[a] Proportional to the reciprocal of symmetry no. (see ref 21).

Table XIII. Activation Energy Barriers by ^{1}H NMR for Conformational Processes in Hexahydrotetrazines[a]

Compd			Δ_{AB}	J_{gem},	T_c,	$\Delta G_c^{\ddagger}$,
No.	Ring	Substituent	ppm	Hz	K	kcal mol^{-1}
1	Mono	Me_4	0.65	12.0	254	11.8 ± 0.2
2	Mono	Et_4	1.66	12.0	226	10.5 ± 0.2
3	Mono	*i*-Pr_4	0.17	12.0	211	10.3 ± 0.2
4	Mono	Bz_4	0.51	11.0	244	11.5 ± 0.2
5	Mono	Me_2Bz_2; sym	0.53	7.5	251[b]	12.1 ± 1.0
16	Tri	Sat	0.38	9.0	370	18.4 ± 0.2
14	Tri	Unsat	1.53	11.5	303	14.2 ± 0.2

[a] Solvents are as for the corresponding compounds in Table I. [b] Large error; much overlap at coalescence.

W. The balance is here a more subtle one, and it is still not completely clear why the tetramethyl compound takes up conformation W, the tetrabenzyl derivative conformation X, while the tetraethyl- and the dibenzyldimethyl derivatives occur as mixtures of X and W.

Barriers to Nitrogen Inversion. The barriers to nitrogen inversion have been calculated using the coalescence temperature approximation for some of the hexahydro-*s*-tetrazines (Table XIII). The barriers for the monocyclic hexahydrotetrazines are all in the region 10–12 kcal mol^{-1}; such differences between them as occur, for example the lowering of barrier between the tetramethyl and tetraethyl compounds, are due probably to raising of the ground state energy in the tetraethyl compound. The two tricyclic compounds display significantly higher barriers, due probably to increased strain in the transition state; that of the saturated compound is again significantly higher than that of the bisolefinic. The sp^2 hybridization in the latter probably results in the transition state being raised somewhat less in energy than in the case of the saturated compound.

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Conformations of Methylated Cycloheptanones

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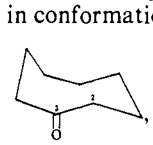
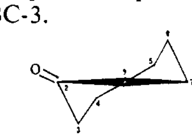
Abstract: ^{1}H NMR studies of dimethylcycloheptanones at low temperatures (below coalescence) together with conformational calculations using the PCILO approach indicate that the most stable conformations are twist chairs with the carbonyl group located at position 2 (i.e., TC-2,1, TC-2,4, and TC-2,5) in accord with a greater competitive conformational preference for the carbonyl group relative to the gem-dimethyl group. The above conclusion is then used to rationalize the low-temperature spectral behavior observed for two tetramethylcycloheptanones. A consistent conformational rationale, which explains all the experimental results, is formulated.

Knowledge of the conformational dynamics of a wide variety of cyclic ketones has constituted a research objective of considerable popularity over the years. Although it has been known for quite a while that both cyclohexane and cyclohexanone have similar overall chair conformations,[2] the extent of flattening caused by the carbonyl group was determined not long ago.[3] The free energy barriers for ring inversion in cyclohexanone[4] and its derivatives[5,6] have been found recently to be much smaller than that of cyclohexane and were rationalized in terms of a lower torsional energy requirement for partial rotation about the bonds next to the carbonyl group. Further insight into the conformational effect of a carbonyl group has been provided from dynamic nuclear magnetic resonance (DNMR) studies of cyclooctanone[7] whose conformation has been found to be similar to the boat-chair of cyclooctane with the carbonyl group located preferentially at position 3 as in conformation BC-3.


BC-3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