a complex mixture of dimer, trimers, and tetramers under forcing conditions.

Even though the formation of dimers in some cases supports the electron-transfer mechanism, one cannot rule out completely the simple hydride reduction of polar intermediates as demonstrated in Scheme IV. It is not unlikely that both mechanisms are operating, depending on the nature of the substrate.

Zinc iodide thus appears to be an effective coreagent with sodium cyanoborohydride because it is a sufficiently strong oxygenophile to function first as a Lewis acid to catalyze the reduction steps and finally to form the very stable zinc oxide in the last step.

Experimental Section

Proton nuclear magnetic resonance spectra were obtained on a Varian EM390 spectrometer, and infrared spectra were measured on a Perkin-Elmer 681 spectrophotometer. Reported boiling points are those observed during distillation with a Kugelrohr apparatus and are uncorrected. Melting points were measured on a Buchi 510 melting point apparatus. Low-resolution mass spectral analyses were performed by the Morgan-Schaffer Corporation, Montreal, and elemental analyses were performed by Guelph Chemical Laboratories Ltd, Guelph, Ontario. All reactions as well as column chromatography were monitered routinely with the aid of thin-layer chromatography using precoated silica gel GF plates (Analtech).

Sodium cyanoborohydride and zinc iodide (98+%) were purchased from Aldrich Chemical Co, Ltd, and were used without purification. Dichloroethane was used without purification. Most of the compounds used in this study were commercial products, and some compounds were prepared from known procedures. The products obtained were readily available materials in most cases. If not, identification was based on ^{1}H NMR, IR, mass spectra, and elemental analyses.

Since the reactions performed are all similar in many aspects, a typical reaction is describe as a specific example.

Method A: Preparation of 4-Propylanisole. To a stirred solution of 4-methoxypropiophenone (1.64 g, 10 mmol) in 1,2-dichloroethane (50 mL) at room temperature were added solid zinc iodide (4.8 g, 15 mmol) and sodium cyanoborohydride (4.7 g, 75 mmol). The reaction mixture was stirred at room temperature for 20 h. It was then filtered through Celite. The Celite was washed with dichloromethane (100 mL). The combined filtrate was evaporated to dryness, and the residue was distilled, bp 100 °C (20 mm), to yield 4-propylanisole (1.23 g, 82%), identical with an authentic sample on the basis of IR, TLC, mass spectrum, ^{1}H NMR data.

Method B: Preparation of 4-Nitrotoluene. To a solution of 4-nitrobenzaldehyde (1.51 g, 10 mmol) in 1,2-dichloroethane (50 mL) at room temperature were added solid zinc iodide (4.8 g, 15 mmol) and sodium cyanoborohydride (4.7 g, 75 mmol). The reaction mixture was refluxed for 20 h. It was then cooled and poured into an ice-cold mixture of saturated ammonium chloride solution containing 10% by volume of 6 N HCl (200 mL). The mixture was extracted with ethyl acetate. The combined extracts were dried over anhydrous magnesium sulfate, filtered and evaporated to dryness. The residue was chromatographed on silica gel, eluting with 20% ethyl acetate in hexane and gave 4-nitrotoluene (330 mg, 24%), 4-nitrobenzyl alcohol (300 mg, 20%), and 4-methyl aniline (118 mg, 11%). The IR, ^{1}H NMR, TLC, and mass spectral data of each products agreed with those of authentic material.

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The Question of Homoaromaticity in 1,6-Dihydro-1,2,4,5-tetrazines

Colin Peter Ronald Jennison, Donald Mackay,* Kenneth Norman Watson, and Nicholas J. Taylor

The Guelph Waterloo Center for Graduate Work in Chemistry, Chemistry Department, University of Waterloo, Waterloo, Ontario, Canada

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1,6-Dihydro-1,2,4,5-tetrazines exist as rapidly interconverting boat conformations in solution. In the 3,6-dimethyl derivatives alkylated on N_1 with small or medium-sized groups the equilibrium is strongly biased toward the conformation with C_6-Me endo, but in the *N-tert*-butyl derivative the opposite conformation is completely dominant. ^{1}H NMR spectroscopy shows the C_6 endo substituents to be strongly shielded and the exo substituents to be strongly deshielded. The individual conformations thus have dramatically different spectra (e.g., **6** has δ_H, δ_{Me} 2.08, 1.93; **9** has δ_H, δ_{Me} 6.00, 0.71). The conformational balance is about equal in the tri-isopropyl compound **30** whose time-averaged C_6-H absorption at δ 3.87 (298 K) separates into two absorptions at δ 5.40 and 2.53 below 190 K. If the N_1 substituent, regardless of its size, is conjugatively electron withdrawing, only the conformation with C_6-H exo is detectable (δ typically 6.2 to 6.7). Since 1-acetyl-1,6-dihydro-1,2,4,5-tetrazine (**32**), whose two boat conformations must be equally populated, shows no resolution of these down to 173 K the inversion barriers must be very much lower in the *N*-acyl than in the *N*-alkyl derivatives. Crystal structure determinations of 1-(hydroxymethyl)- and 1-acetyl-3,6-dimethyl-1,6-dihydro-1,2,4,5-tetrazines (**5** and **14**) confirm the opposite arrangements of the C_6 substituents in the boat conformations. Despite the nonplanarity of the five atoms N_1 to N_5 and the relatively large separations between N_1 and N_5 (2.29 Å in **5** and 2.35 Å in **14**), we suggest that a case can be made for the operation of a homoaromatic ring current in these systems to account for the remarkable proton shielding and deshielding observed.

Introduction

Recently, van der Plas and co-workers have described a remarkable NMR shielding of a proton on C_6 in the low temperature spectrum of 1,6-dihydro-1,2,4,5-tetrazines (**1**), an effect they attributed to homoaromaticity.[1-3] They supposed that C_6 was out of plane with respect to a planar array of the other five ring atoms, which were capable of sustaining a ring current and thus shielding the C_6 proton above them. Such a homotetrazole arrangement is depicted in **2**.

(1) Counotte-Potman, A.; van der Plas, H. C.; van Veldhuizen, B *J. Org. Chem.* **1981**, *46*, 2138.

(2) Counotte-Potman, A.; van der Plas, H. C.; van Veldhuizen, B *J. Org. Chem.* **1981**, *46*, 3805.

(3) Counotte-Potman, A.; van der Plas, H. C.; van Heldhuizen, B.; Landheer, C. A. *J. Org. Chem.* **1981**, *46*, 5102.

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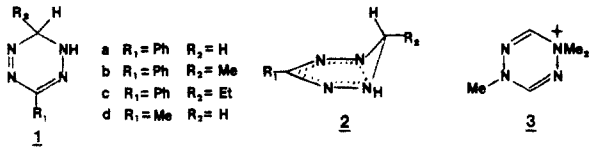


1 2 3

Implicit in such a picture is the requirement of shorter C–N and N–N and longer C=N and N=N bonds than the simple valence bond formula **1** would imply, and, of crucial importance, an unusually short N_1 to N_5 distance. All these features can be simply tested for by an X-ray analysis. Later the Dutch group carried out a crystal structure determination on the tetrazine **1c**.[4] They found, in fact, that it was boat shaped. The N_1 to N_5 distance (2.29 Å) suggested only a slight degree of transannular bonding. Using standard crystallographic bond lengths[5] for C to C, C to N, and N to N bonds as a function of bond order (from 1 to 2), they noted that all bonds between atoms N_1 through N_4 were delocalized. They concluded, on balance, that their results were "not in conflict" with their previous proposal of homoaromaticity.

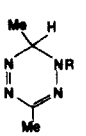
In related work by Olofson and co-workers, a similar shielding (δ 3.35) was noted for the quaternary Me protons in the 1,1,4-trimethyl-1,4-dihydro-1,2,4,5-tetrazinium cation (**3**).[6] This was also attributed to the operation of a ring current round the five atoms flanking the positive N in what they presumed was a planar six-membered ring. Subsequently,[7] an X-ray analysis of the fluoroborate of **3** showed the cation to be boat shaped like **1c**. N_4 was almost trigonal and delocalization through N_4–C_3–N_2 was evident from the bond lengths. The N_2–C_6 distance of 2.41 Å again argued against much bonding between these atoms. The authors were noncommittal in regard to the question of homoaromaticity.

These results, especially those of the Dutch group, require us to report our own observations on the 1,6-dihydro-1,2,4,5-tetrazine system.

Discussion

A few years ago we observed that the C_6-methyl and methine protons in 3,6-dimethyl-1,6-dihydro-1,2,4,5-tetrazine (**4**) resonated at about the same frequency in a complex absorption near δ 2.0[8] (resolved at 400 MHz: d, q δ 1.94, 2.13). This intense shielding of the methine proton was also found in its *N*-hydroxymethyl, (**5**) and *N*-methyl (**6**) derivatives, and we concluded, as the Dutch group had done,[1] that we had encountered a homoaromatic system with the conformation **2** (R_1 = R_2 = Me), the C_6 alkyl group being in the intrinsically more stable exo position.

	R		R
4	H	13	CHO
5	CH_2OH	14	COMe
6	Me	15	$COCMe_3$
7	Et	16	CO_2Me
8	$CHMe_2$	17	CONHPh
9	CMe_3	18	CSNHPh
10	$CHEt_2$	19	$SO_2C_6H_4Me$-p
11	$CH_2C_6H_4Br$-p		
12	$CHPh_2$		



We further supposed that the analogous *N*-acyl derivatives might fail to show this effect, since the competitive delocalization of the nitrogen lone pair, necessary for the aromatic sextet, could destroy the homoaromaticity. The *N*-acetyl derivative **14**, however, showed shielding, not of the methine (δ 6.69), but of the methyl protons (δ 1.00), suggesting again a geometry like **2**, with R_2 and H groups exchanged in position. To confirm this conformational difference between the acylated and nonacylated derivatives, as well as the other structural features predicted above for a homoaromatic system, we carried out X-ray

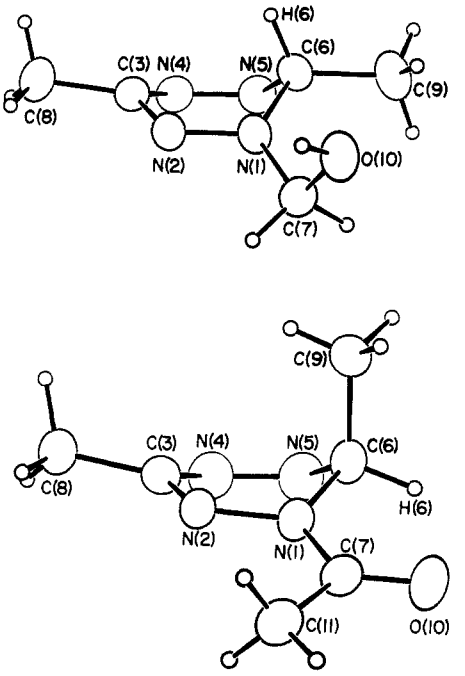


Figure 1. ORTEP plots of 1-hydroxymethyl-3,6-dimethyl-1,6-dihydro-1,2,4,5-tetrazine (**5**) (upper), and 1-acetyl-3,6-dimethyl-1,6-dihydro-1,2,4,5-tetrazine (**14**) (lower).

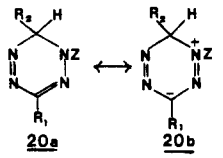
Table I. Bond Lengths (Å), Bond Angles (deg), and Some Intramolecular Contacts of Interest in Compounds 5 and 14

	5	14
	Bond Lengths	
N(1)–N(2)	1.325 (2)	1.373 (2)
N(2)–C(3)	1.314 (2)	1.287 (3)
C(3)–N(4)	1.381 (2)	1.416 (3)
N(4)–N(5)	1.270 (2)	1.256 (3)
N(5)–C(6)	1.478 (2)	1.487 (3)
C(6)–N(1)	1.438 (2)	1.384 (3)
N(1)–C(7)	1.457 (2)	1.384 (3)
C(3)–C(8)	1.490 (2)	1.485 (3)
C(6)–C(9)	1.504 (2)	1.507 (3)
C(7)–O(10)	1.395 (2)	1.215 (3)
C(7)–C(11)		1.488 (3)
N(1)···N(5)	2.285 (2)	2.349 (3)
N(2)···N(4)	2.324 (2)	2.372 (3)
N(1)···H(6)	1.96 (2)	1.97 (2)
N(5)···H(6)	2.01 (2)	2.04 (2)
	Bond Angles	
C(6)–N(1)–N(2)	115.66 (8)	117.78 (10)
N(1)–N(2)–C(3)	114.41 (8)	113.77 (11)
N(2)–C(3)–N(4)	119.12 (7)	122.60 (10)
C(3)–N(4)–N(5)	118.51 (8)	119.42 (12)
N(4)–N(5)–C(6)	112.97 (8)	115.98 (12)
N(5)–C(6)–N(1)	103.17 (6)	106.40 (9)
C(6)–N(1)–C(7)	126.88 (9)	122.29 (12)
N(2)–N(1)–C(7)	117.44 (8)	119.43 (10)
N(2)–C(3)–C(8)	119.20 (9)	120.79 (12)
N(4)–C(3)–C(8)	118.32 (9)	115.54 (13)
N(5)–C(6)–C(9)	110.68 (9)	110.83 (12)
N(1)–C(6)–C(9)	115.17 (9)	113.33 (11)
N(1)–C(7)–O(10)	112.13 (6)	119.53 (10)
N(1)–C(7)–C(11)		116.93 (12)
O(10)–C(7)–C(11)		123.54 (12)

(4) Stam, C. H.; Counotte-Potman, A. D.; van der Plas, H. C. *J. Org. Chem.* **1982**, *47*, 2856.
(5) Burke-Laing, M.; Laing, M. *Acta Crystallogr., Sect. B* **1976**, *B32*, 3216.
(6) Kohn, H.; Olofson, R. A. *J. Org. Chem.* **1972**, *37*, 3504.
(7) Hoskin, D. H.; Wooden, G. P.; Olofson, R. A. *J. Org. Chem.* **1982**, *47*, 2858.
(8) Jennison, C. P. R. Ph.D. Dissertation, University of Waterloo, Canada, 1976.

analyses on the *N*-hydroxymethyl derivative **5**,[9] mp 76–77 °C, and the *N*-acetyl derivative **14**, mp 44–45 °C[8] (crystallographic data for **5** and **14** are given in Table I). The two boat-shaped structures are shown in Figure 1, bond lengths and angles are given in Table II (supplementary material), and atomic coordinates and isotropic thermal parameters in Table III (supplementary material). (Tables I–III are in the supplementary material. Table I is an extract from Table II (supplementary material). Structure factor tables are available directly from the author.)

The degree of puckering in **5** (49.8° at sp^3C, 25.3° at sp^2C) is almost identical with that in **1c** (49.3°, 26.7°),[4] as are the ring bond lengths with the exception of N_1 to N_2 and N_2 to C_3, which are significantly longer and shorter respectively in **5**. The delocalization in N_1 to C_3 is thus greater in **1c**. Though the phenyl ring of **1c** was found to be not quite in plane with these atoms (by 19°), some of this delocalization may nevertheless arise from extended conjugation with the phenyl group, as well as from resonance effects within the heterocyclic ring (**20a** ↔ **20b**).



20a **20b**

As expected from its NMR spectrum, the *N*-acetyl compound **14** has the C_6-Me group in the endo (shielded) position. The boat is shallower than that of **5** (41.6°, 18.4°). Delocalization between N_1 and C_3 is even less than in **5**, the bond lengths of N_1 to N_2 and N_2 to C_3 being very close to those for pure single and double bonds, respectively,[5,10] and consistent with the negligible contribution expected from resonance form **20b** (Z = COMe).

The N_1 to N_5 distances, 2.285 Å in **5** and 2.349 Å in **14**, are very close to those observed in **1c**[4] and **3**.[7]

Attention here, as in earlier work[1-4,6,7] has focussed on shielding effects, that is on the methine proton in **1**, **4**, or **5**, or the methyl protons in **14**. As might be assumed, however, a deshielding region exists in these 1,6-dihydrotetrazines, and we wish to try to delineate both these regions using the above examples, as well as a wide range of N_1- and C_6-substituted derivatives.

The magnitude of the shielding in **4** can be roughly gauged by comparing the observed values with those of the C_6 protons in suitable models, the hexahydrotetrazine **21**[11] and the tetrahydrotetrazines **22** and **23**,[9] shown in Figure 2. Using the incremental downfield shifts created by the double bonds α,β and β,γ to C_6, an absorption at δ 4.0–4.5 would be expected, in the absence of anomalous NMR effects, for the methine proton in **4**, which is thus shielded by over 2 ppm.[12] This estimate accords well with the fast exchange CH_2 absorption of **1d**,[13] at δ 3.94[1], as does the observed value for the methine proton of **4** at δ 2.13 with the slow exchange shielded absorption of **1d** at δ 2.04.

The shielding of the C_6 Me in **14** is harder to determine, since not much data on acylated tetrazines is available, but inspection of compounds **22**, **23**, and its acetylated derivative **24** (Figure 2) suggests an absorption at δ 1.6–1.8 would be reasonable. This shielding of over half a ppm is remarkable given that the protons are one bond further removed from the ring surface than the C_6 H in **4** and are two-thirds of the time outside the effective shielding region. A measure of the shielding is the fact that the chemical shift of the C_6 methyl group in **14** is the same as that in **21**, of which **14** is an acetylated and doubly unsaturated derivative!

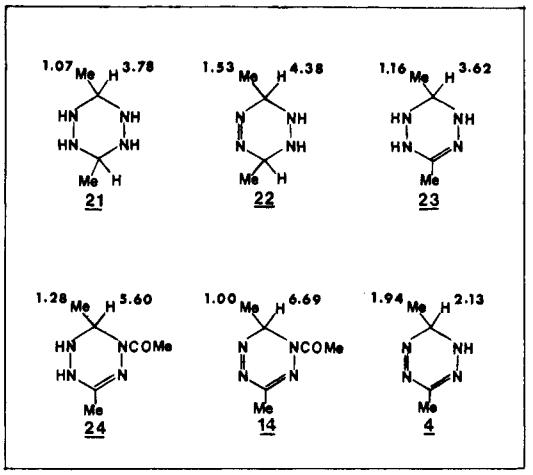


Figure 2. C_6 methyl and methine proton shifts in representative model compounds.

Inferred perhaps, but certainly not emphasized,[2] is the *deshielding* observed at slow exchange in the exo proton of **1d** at δ 5.84.[14] Since the fast exchange value of the methylene protons is close to "normal", the exo proton is thus about as deshielded as the endo is shielded.[15]

From the compounds of Figure 2, a prediction of δ 1.5–1.7 can be made for the C_6-Me absorption of **4**, which is thus substantially deshielded. Compounds **22–24** suggest that the methine (exo) proton in **14** should have an absorption rather close to the *observed* value (δ 6.69), and that sources of deshielding other than the carbonyl group are unimportant. This is misleading. The exo absorption of **1d** (δ 5.84) and work to be described below establish beyond any doubt that most of the downfield shift observed for the methine proton in **14** is due to the deshielding effect characteristic of this particular ring system. A C_6 exo proton on *any* 1,6-dihydro-1,2,4,5-tetrazine is strongly deshielded.

We have synthesized a range of N-alkylated derivatives of **4**, the tetrazines **5–12**. They were made in modest yields (ca. 50% after chromatography) by alkylation (bromide or iodide) either of **4**, in acetone, or of its lithium salt, in ethanol, in the presence of K_2CO_3. They were rather unstable at room temperature, and it was not in general possible to obtain either elemental or mass spectroscopic analyses for them. Their identity follows from the characteristic features of their ^1H NMR spectra, which are listed in Table II.

Using standard procedures we have prepared in good yields acyl (**13–15**), the methoxycarbonyl (**16**), a carbamoyl (**17**), a thiocarbamoyl (**18**), and the tosyl (**19**) derivatives. Their proton shifts are listed in Table III. The NMR spectra of all the 1,2,4,5-tetrahydrotetrazines in Tables II

(9) Skorianetz, W.; Kovats, E. sz. *Helv. Chim. Acta* **1972**, *55*, 1404.
(10) The published values in ref 5 are generalized from models which may not be fully appropriate for the tetrazines.
(11) Skorianetz, W.; Kovats, E. sz. *Helv. Chim. Acta* **1970**, *53*, 251; the tetrahydrate was dried over P_4O_{10} and its spectrum run in $CDCl_3$.
(12) This additive analysis is an oversimplification if only in that it ignores the possible effects of conjugation in **4**.
(13) This simply says that the fast exchange absorption is in the normal expected range. NMR solvent differences (CD_3OD–D_2O used in ref 1) and the expected chemical shift differences between a CH_2 and a *CH*Me add to the qualitative nature of the comparison.
(14) Are there any examples of larger geminal methylene shifts in neutral organic molecules than those recorded[1] for **1**, 4.0 ppm in **1a** and 3.8 ppm in **1d**?
(15) In cation **3** the quaternary methyl resonances give a time averaged singlet, down to 223 K at least, at the considerably shielded value of δ 3.35. Clearly one methyl group in this case is, on average, in a region which is not, or is only slighly, deshielded.

Table II. Synthesis and ^1H NMR Spectra of N_1-*R*-3,6-Dimethyl-1,6-dihydro-1,2,4,5-tetrazines (R = alkyl)

			^1H δ ($CDCl_3$)[a]			
compd	R	method[b]	C_6 Me	C_6 H	C_3 Me	R
4	H	ref 11	1.94	2.13	2.49	6.3 (b)
5	CH_2OH	ref 9	1.85	2.64	2.40	3.36 (OH), 4.83 (CH_2)
6	Me	A	1.93	2.08	2.44	3.22
7	Et	A	1.88	2.33	2.41	1.04 (CH_3, t, J = 7.1), 3.41 ($CHCH_3$, m), 3.51 ($CHCH_3$, m)
8	$CHMe_2$	A	1.72	2.74	2.42	0.97 (CH_3, d, J = 6.5), 1.39 (CH_3, d, J = 6.6), 3.65 (CH, m)
9[c]	CMe_3	B	0.71	6.00	2.41	1.32
10	$CHEt_2$	B	1.73	2.65	2.41	0.53 (CH_3, t, J = 7.4), 0.8 (CH_2, m), 0.96 (CH_3, t, J = 7.5), 1.3 (CH_2, m), 3.46 (CH, m)
11	p-$BrC_6H_4CH_2$	A	1.80	2.56	2.49	4.60 (CH_2), 6.95, 7.42 (4 H, q, arom)
12	$CHPh_2$	A	1.58	3.28	2.43	5.84 (CH, s), 6.8–7.0 (2 H, m, o-Ph), 7.1–7.3 (3 H, m, (m + p)-Ph), 7.35 (5 H, bs, Ph)

[a] C_6 Me(d) and C_6 H(q) are first order in some cases only at 400 MHz; C_3 Me is a singlet. [b] For methods A and B see experimental section; RI was used for **6–10**, RBr for **11** and **12**. [c] Prisms from pentane, melting at ambient temperature. Anal. Calcd for $C_8H_{16}N_4$: C, 57.11; H, 9.59; N, 33.30. Found: C, 57.03; H, 9.50; N, 33.52. The sample was stored at −10 °C until the time of analysis.

Table III. ^1H NMR Spectra and Elemental Analyses of N_1-Acyl-3,6-dimethyl-1,6-dihydro-1,2,4,5-tetrazines (R = acyl)

			^1H δ ($CDCl_3$)[a]					calcd / found		
compd	R	mp, °C	C_6 Me	C_6 H	C_3 Me	R	Anal.	C	H	N
13	CHO	oil	1.13	6.41	2.59	8.63	$C_5H_8N_4O$	42.85	5.75	39.98
								42.86	5.80	40.32
14	COMe	44–45[b]	1.00	6.69	2.57	2.35	$C_6H_{10}N_4O$	46.75	6.49	36.36
								46.31	6.33	35.88
15	$COCMe_3$	oil	0.97	6.66	2.56	1.34	$C_8H_{16}N_4O$	55.08	8.22	28.54
								54.96	8.22	28.89
16	CO_2Me	49–51[b]	1.08	6.45	2.60	3.92	$C_6H_{10}N_4O_2$	42.35	5.88	32.94
								42.14	5.88	33.02
17	CONHPh	81–82[c]	1.03	6.72	2.62	7.1–7.6 (5 H, m, Ph), 8.45 (NH, b)	$C_{11}H_{13}N_5O$	57.13	5.67	30.28
								56.96	5.89	30.31
18	CSNHPh	75–76[b]	1.06	*d*	2.59	7.1–7.7 (6 H, m, Ph + C_6 H), 8.44 (NH, b)	$C_{11}H_{13}N_5S$	53.42	5.30	28.32
								53.33	5.20	28.54
19	p-$SO_2C_6H_4Me$	78–79[c]	1.01	6.25	2.51	2.42 (Me), 7.28, 7.71 (4 H, q, arom)	$C_{11}H_{14}N_4O_2S$	49.61	5.30	21.04
								49.66	5.28	21.17

[a] C_6 Me(d), C_6 H(q), C_3 Me(s). [b] From hexane. [c] From aqueous MeOH. [d] Hidden by aromatic protons.

and III provide immediate and unmistakeable proof of the dominant conformation of the molecule, namely the C_6-methyl and methine absorptions close together in the exo-methyl conformation or widely separated in the endo-methyl conformation. With one exception, all the tetrazines fall neatly into one or other of the two conformational types. N_1 unsubstituted or N_1 alkylated tetrazines have the C_6-methyl group predominantly exo, and those with nitrogen substituted with conjugatively unsaturated groups have the methyl group endo.

The exception is the *N-tert*-butyltetrazine **9**. Its C_6 absorptions (δ: C_6 Me 0.71, C_6 H 6.00) and those of the *N*-methyltetrazine **6** (δ: C_6 Me 1.93, C_6 H 2.08) are shown in Figure 3. These vividly different spectra for such simple closely related substances serve also to illustrate the differences between the NMR spectra of all the other tetrazines in Table II and those of the tetrazines in Table III.

A slight but significant trend is observed in **6–8** as the substituent increases in bulk from methyl to ethyl to isopropyl. The methine proton resonates at increasingly lower field, while the methyl protons show the opposite effect, though of course to a lesser extent. These results, and the values for the *tert*-butyl derivative, together with the fact that only one shift is observed in every case for each set of protons, lead unequivocally to one conclusion. In all the *N*-alkyltetrazines the two boat conformations are in rapid equilibrium at room temperature,[16] with the methyl (**6**) and the *tert*-butyl (**9**) derivatives predominantly in opposite conformations, **25** and **26** (C_6 Me exo and endo respectively), while the ethyl (**7**) and *iso*-propyl (**8**) derivatives have increasing amounts of the minor conformation **26** populated.[17]

That the conformations in solution are boat-shaped as they are in the crystal is almost certainly assured by the observation that the ^{13}C NMR spectrum of **5** in $CDCl_3$ solution is identical with that found with the magic angle spinning technique using crystalline **5**.

While conformational preference is completely determined by steric effects in the case of *N*-alkyl derivatives, this is certainly not so for tetrazines substituted with conjugatively unsaturated groups. Regardless of size (cf. **13** vs **15**) there is an overwhelming bias towards the conformation **26**. This is borne out by the relative constancy of the C_6-methyl shifts (δ 0.97–1.13) and the methine shifts (δ 6.41–6.72) in the acyl derivatives, **13–17**.[18]

The C_3-methyl group seems to be quite insensitive to shielding and deshielding effects. In **4**, and its fifteen

(16) This is at variance with the interpretation of the spectrum of the closely related C_6-alkyl derivatives **1b** and **1c**,[1] which were judged not to invert at room temperature. There is no reason to believe that **1b** and **1c** should have a much higher conformational barrier than that of **1a** or **1d** or any of the alkylated derivatives reported here.

(17) Since the values in Table II for **6** and the parent compound, (**4**) are very close, they suggest that the conformational preference for these is almost completely C_6 methyl exo, i.e., **25**. It is also likely that the *tert*-butyl derivative (**9**) is almost completely in conformation **26**. The crystal structure of **5** and **14** show that the C_6 exo and the N_1 substituents are nearly eclipsed, an intolerable arrangement in conformation **25** when R is *tert*-butyl. The closeness of the methine shift in **9** to that of the exo proton in **1d** is significant. The methine shifts in **6** and **9** must be close to the limiting values for each conformation.

(18) Comparison of these values with those of **1d** or **9** suggests that the carbonyl group contributes an intrinsic deshielding of about half a ppm to the methine proton. The methine absorption in **18** was hidden in the aromatic region. The origin of this additional deshielding is unknown.

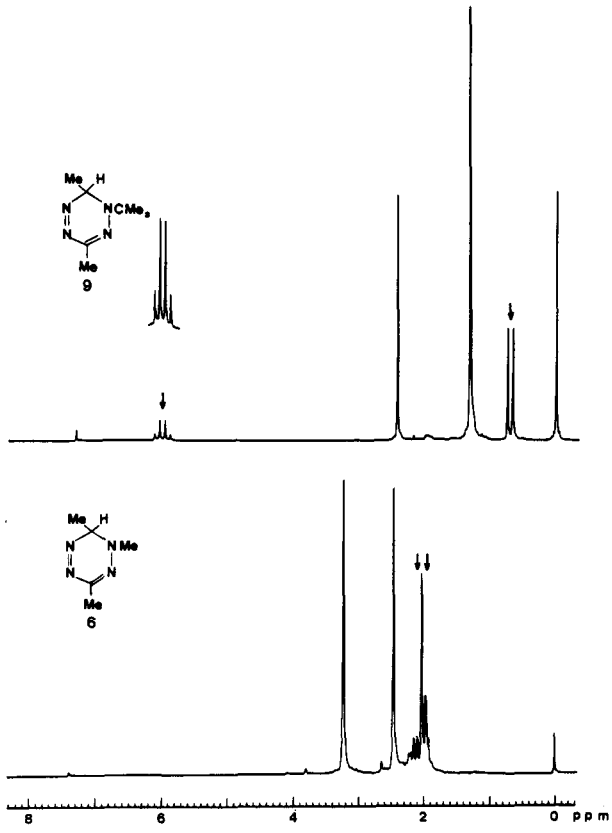
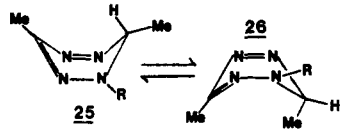


Figure 3. 80-MHz ^1H NMR spectra of 1-methyl- and 1-*tert*-butyl-3,6-dimethyl-1,6-dihydro-1,2,4,5-tetrazines (**6** and **9**), lower and upper, respectively. The arrowed absorptions are those of the C_6 H (downfield) and the C_6 Me.

derivatives described here, this methyl group resonates within a very narrow range, δ 2.4–2.6.

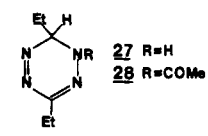
We assumed that the barriers to inversion in **4** and its *N*-alkyl derivatives would be comparable to those of the C_6 unsubstituted analogues **1**. The enantiomeric conformations of the latter were readily frozen out in dynamic NMR experiments; in the case of **1d** a $\Delta G^{\ddagger}$ of 11.8 ± 0.5 kcal mol^{-1} at 233 K was found.[1] To observe such a barrier in an alkyl derivative of **4** we required a compound in which a sufficient concentration of the minor conformation **26** was present that its absorptions would be detectable when peak separation occurred.[19] In the ideal case, if the conformations of **25** and **26** were equal, the room temperature methine absorption would be expected around δ 4.0. This clearly required an alkyl group on nitrogen sterically more demanding than isopropyl (δ C_6 H, 2.73), but much less so than *tert*-butyl (δ 6.00).

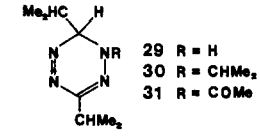


If the four C_6-proton absorptions in the conformational mixture of **25** and **26** were frozen out, three would appear in a narrow region upfield, one methine (δ ca. 1.0 in **25**) and both methyl groups (δ ca. 1.0 in **26** and 2.0 in **25**). These would be obscured by one another, and in some cases by peaks from the *N*-alkyl group. The search in the low temperature spectrum would have to concentrate on the methine quartet of conformation **26** near δ 6.0. From the list in Table II the most promising candidates for a detectable amount of conformation **26** are the isopropyl (**8**), the 3-pentyl (**10**), and the benzhydryl (**12**) derivatives. All failed to show the required low temperature quartet down to 213 K.

Variable-temperature ^{13}C NMR spectroscopy seemed superficially promising. Peak interference is not a problem, any peak is potentially capable of separation from all others, and very small barriers can be frozen out. The spectrum of **10** below 260 K showed clean separation of the ring C_3 carbon into two peaks in a ratio of ca 2:1.[20] In **12**, one phenyl carbon showed a doublet below 273 K, and both methine peaks and the C_6-methyl peak began to broaden below 240 K, but were not further resolved down to 173 K. Each of these compounds shows clear evidence of conformation separation. However, each of these compounds also has a bulky substituent containing two diastereotopic groups. N_1–C rotation leads to three rotamers of different energy, independent of boat–boat interconversions, and the ^{13}C spectra do not allow a distinction between the two types of conformational exchange.[22] Detection of the equilibrium **25** ⇌ **26** is only possible by a technique which characterizes each of them unambiguously, namely ^1H NMR spectroscopy.

By suitable modification we were able to extend the aldehyde route to **4**[11] and the diethyl derivative **27**[23] to give the diisopropyl derivative **29**. The hexahydrotetrazine required for oxidation to **29** was obtained in only poor yield by the dimerization of isobutyraldehyde hydrazone at 263 K.[24] Pivaldehyde hydrazone failed to dimerize, so a synthesis of 3,6-di-*tert*-butyl-3,6-dihydro-1,2,4,5-tetrazine was not possible. The C_6 absorptions in **27** (CH_2 m *downfield* of CH t: δ 2.30, 1.98) and in **29** ($CHMe_2$ m *downfield* of ring CH d: δ 2.53, 1.71)[25] show clearly that they are mainly in the endo C_6-H conformation **25**; their *N*-acetyl derivatives **28** (CH *dd*: δ 6.64) and **31** (CH d: δ 6.38) are in the opposite conformation. The spectra of the diethyl compounds **27** and **28** are shown in Figure 4.





We assumed that **29** would be the best starting point for making an alkylated tetrazine with the right amount of crowding. Our first choice of N_1 substituent was the isopropyl group: the desired result was achieved. The triisopropyltetrazine **30** showed (CD_3COCD_3, 400 MHz) at 298 K a slightly broadened[26] doublet at δ 3.87 for the

(19) The problem in detecting a conformation in low concentration is compounded by the fact that as the temperature is lowered, the population bias towards the major conformation grows (Boltzman effect).

(20) The conditions necessary to quantify the data were not met, especially for a non-hydrogen bearing carbon, and the ratio may not be significant.[21]

(21) Shoolery, J. N. *Prog. NMR Spectros.* **1977**, *11*, 79. Mann, B. E. *Prog. NMR Spectros.* **1977**, *11*, 95.

(22) The fairly bulky group ideal for ^{13}C NMR work is neopentyl. Though its methylene protons are diastereotopic when the group is attached to N_1, its methyl carbons are isochronous by rotation. We failed however to obtain any neopentyltetrazine when neopentyl bromide was treated with either **4** or the lithium salt of **4**.

(23) Skorianetz, W.; Kovats, E. *Helv. Chim. Acta* **1971**, *54*, 1922.

(24) There is likely an equilibrium between hydrazone and dimer, since further crops of the latter could be obtained from the filtrate. In the case of less bulky hydrazones dimerization is very efficient.

(25) The shielding of this doublet at δ 1.71, should be viewed alongside the absorption of the methine doublet at δ 3.40 in its saturated precursor 3,6-diisopropylhexahydro-1,2,4,5-tetrazine.

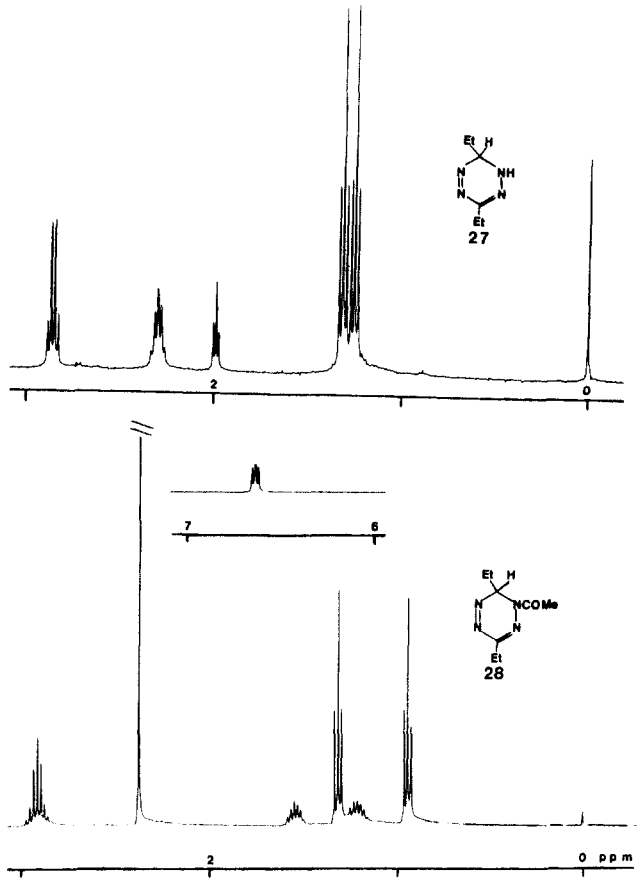
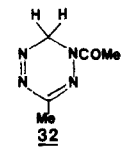


Figure 4. 400-MHz ^1H NMR spectra of 3,6-diethyl-1,6-dihydro-1,2,4,5-tetrazine (**27**) and its N_1-acetyl derivative **28**. As well as the highly shielded and deshielded C_6 H in **27** and **28** (1.98 and 6.64 respectively), note the C_6 ethyl group in **28** (0.94, 1.21, 1.55) *upfield* of that in **27** (1.25, 2.30).

C_6-methine proton. On cooling, this peak became lost in the baseline by 230 K, reemerged by 190 K as two broad absorptions, and finally, at 163 K, as a sharp doublet at δ 5.40 and a broad[26] peak at δ 2.53. Representative spectra from this study are shown in Figure 5 (Supplementary material). Complementary evidence for the freezing of the two conformations was evident in other parts of the spectrum. The N_1 and C_6 isopropyl methyl doublets broadened and then sharpened into a complex set of sharp doublets on cooling; similarly the C_3-methine absorption changed from one sharp multiplet at δ 3.07 to two, at 3.13 and 3.03. Though no attempt was made to measure them exactly, the areas of the peaks at δ 5.40 and 2.53 were comparable[29] (as were those at 3.13 and 3.03) indicating that both conformations of **30** are about equally populated.[30]

The shielding and deshielding of the C_6 proton in the frozen spectrum of **30** are rather less (by ca. half a ppm) than observed in the frozen spectrum of **1a**, or in the room-temperature spectra of the highly conformationally biased **4** or **6** (endo C_6 H) or **9** (exo C_6 H). This suggests that **30** exists in flatter boat forms than the other tetrazines, thus reducing the penetration of the C_6 substituents into the shielding and deshielding zones. A flatter boat relieves isopropyl–isopropyl repulsions, between C_6 and N_1 in conformation **25**, and C_6 and C_3 in conformation **26**.

The methyl peaks in the spectrum of the *N*-acetyl derivative **14** remained sharp down to 163 K, which can be explained either by very low barriers between conformations, or by the presence of mainly one conformation in solution; the ^{13}C spectrum similiarly showed no change down to 183 K. Acetyl rotation and boat equilibration (**25** $\rightleftharpoons$ **26**) are therefore very fast and/or conformationally very biased. The latter is certainly true, on the NMR evidence, for boat equilibration in all the conjugatively usaturated derivatives, **13–19**. The situation is simpler if the C_6 substituents are the same, since the boat conformations are then enantiomers and their populations are equal. Accordingly we synthesized[1] and acetylated **1d**, but found that the methylene and methyl singlets in **32** also remained



sharp down to 173 K (80 MHz), showing that the racemization of **32** is very much faster than that of **1d** (again acetyl rotation is fast or one rotamer is dominant).[32] It seems likely then that all *N*-acyl-1,6-dihydrotetrazines invert very rapidly, though we have no explanation for why their inversion barriers are so much lower than for the *N*-alkyl counterparts.

As well as the shielding and deshielding effects described for the C_6-methyl and methine protons in the tetrazines **4–19**, large diastereotopic shifts were frequently noticeable in the N_1 alkyl group, and in the ethyl and isopropyl compounds **27–31**. In all of these, one diastereotopic group was generally in a normal position and its partner was strongly shielded. Examples are shown in the assignments in Table II for the isopropyl methyl group in **8** and the methyl and methylene pairs in the 3-pentyl group in **10** (no implication is intended as to which group is which).

(26) At 400 MHz the C_6-methine proton in all the alkylated (but not the acylated) dihydrotetrazines showed considerable line broadening, but was fairly sharp at 80 MHz. The broadening is almost certainly due to chemical exchange, well above the coalescence temperature, but below the very fast limit where the line widths are square field dependent.[27] Notable is the fact that **6** shows the effect but **4** does not. The *only* conformational process between different energy species possible in those is **25** $\rightleftharpoons$ **26**. One explanation is that **4** has essentially none of conformation **26** present, while **6** has a small amount. The problem is thus one of 'hidden partner exchange'.[28] Even 2% of conformation **26** in **6** would cause a maximum broadening of 23 Hz at 400 MHz, a very noticeable effect. Measurements of broadening are here complicated by the coupling, and we did not in any case do variable temperature NMR work on **6** at 400 MHz.

In the case of **30** the methine absorption at δ 2.53 is still broad at 400 MHz in the conformation **25** in the low-temperature spectrum. This again must be caused by chemical exchange. Its origin is probably hindered rotation between the almost coplanar N_1 and C_6 isopropyl groups. When the C_6-methine proton is in the exo position, in **26**, the rotation is fast, and the low field doublet at δ 5.40 is sharp.

(27) Carrington, A.; McLachlan, A. D. "Introduction to Magnetic Resonance"; Harper and Row: New York, 1967; Ch. 12. Sandstrom, J. "Dynamic NMR Spectroscopy"; Academic Press: New York, 1982; Chapter 2.

(28) (a) Anet, F. A. L.; Basus, V. J. *J. Mag. Reson.* **1978**, *32*, 339. (b) Okazawa, N.; Sorensen, T. S. *Can. J. Chem.* **1978**, *56*, 2737.

(29) Assuming equal concentrations, these shifts require a ΔG^* for the equilibrium of between 10.1 and 8.6 kcal mol^{-1} at the coalescence temperature which is somewhere between 238 K and 203 K. The barrier is thus somewhat lower than that of **1d** ($\Delta G^* = 11.8 \pm 0.5$ kcal mol^{-1} at 233 K).

(30) These low temperature shifts and the high temperature (304 K) time averaged shift at δ 3.87 leads to a weighted value of 53% of conformation **25** in the mixture. However, no significance can be attached to this number. As the solution is cooled, the high temperature absorption drifts slightly *downfield* as it broadens, the wrong direction if **25** is increasing in concentration, as it must on cooling (Boltzmann effect) if it is the major conformation. Thus the C_6-methine shifts are temperature dependent and the normal linear interpolation of shift as a function of concentration[31] cannot be applied.

(31) Eliel, E. L.; Martin, R. J. L. *J. Am. Chem. Soc.* **1968**, *90*, 582.

(32) If the methylene protons in **32** have the same shift difference (3.80 ppm) as in **1d** in the frozen spectrum a value of $\Delta G^* = 7.6$ kcal mol^{-1} at 173 K can be calculated as an upper limit to the racemization barrier.

The benzhydryl compound **12** showed one set of ortho phenyl protons, *upfield* (at δ 6.90) of all the other aromatic protons. The *N*-ethyl derivative **7**, however, showed only a small diastereotopic shift (0.10 ppm) between its methylene protons. From these results it appears that in an N_1 alkyl group one set of diastereotopic protons on a carbon, two atoms or more removed from the ring, can penetrate the shielding zone, either above the ring (like the C_6 substituent), or, more likely, for steric reasons, below it. The shift between the C_6-methylene protons in **27** was not detectable, but was very noticeable (0.34 ppm) after acetylation (Figure 4; note that the C_6-methyl triplet in **27** is *downfield* of the corresponding methyl triplet in its acetyl derivative **28**). Similarly in the diisopropyl compound **29** the C_6 Me pair have the same shift; in the acetyl derivative **31** there is a diastereotopic shift of 0.30 ppm. In the triisopropyl compound **30** all six methyl doublets were observed at fast equilibration of the boat forms; at 163 K, in the frozen spectrum, nine of the twelve methyl doublets were fully resolved without overlap, spread over one ppm, with the most shielded being at δ 0.63.

And what of homoaromaticity? Since Applequist and Roberts first recognized an unusual stabilization in the cyclobutenyl cation[33] and the generalized concept was later formulated by Winstein,[34] much effort has been expended, using theory and experiment, in trying to firmly establish the existence of this phenomenon in cations, anions, and neutral molecules.[35] The most common experimental approach has been spectroscopic, in particular by the observation of shielding–deshielding effects in the NMR spectra, attributed to a ring current, and to a lesser extent by photoelectron spectroscopy.[36] Thermochemical measurements have also been used.[37]

The structural requirement traditionally accepted for (mono) homoaromaticity is the occurrence of $(4n + 2)\pi$ electrons in a continuous, nearly coplanar, array of sp^2 atoms, whose termini are separated by an sp^3 atom, but are sufficiently close that some degree of bonding interaction can be expected across them. The originating p atomic orbitals are nearly orthogonal to the plane, tilted out of parallel only as the deviations from coplanarity of the atoms require.[38] These features can, in general, be properly observed by X-ray crystallography.

Very little X-ray data has, in fact, been published on suitable candidates for homoaromaticity. Carbocyclic examples include the $AlCl_3$ complex of tetramethylcyclobutene ("homocyclopropenium"),[40] 2-hydroxyhomotropylium hexachloroantimonate,[41] and the neutral molecules 1,4,7-cyclononatriene,[42] triquinacene,[43] 6,7-benzoelassovalene,[39] and C_{16}-hexaquinacene.[36e]

The best known and most intensively studied example of homoaromaticity is of course the homotropylium cation. Experimental evidence for it, and to a lesser extent for the homocyclopropenium ion, comes from ^1H NMR spectroscopy,[44-48] and is supported by theoretical studies.[49-54] Calculations have shown that the most stable arrangement of C_1 to C_7 in homotropylium is not planar but boat shaped,[52] a fact confirmed by the X-ray analysis.[41] From the known geometry of the ion the shift difference between the C_8 proton pair, due to both the local carbon atom anisotropies and to the ring current, have been calculated (almost 60% arose from the latter),[55] and found to be in reasonable agreement with the experimental value.[56] The case for cationic homoaromaticity seems to have been conclusively established.

Earlier interpretations of experimental results with anionic systems as indicative of homoaromaticity[57-64] have

(33) Applequist, D. E.; Roberts, J. D. *J. Am. Chem. Soc.* **1956**, *78*, 4012.
(34) Winstein, S. *J. Am. Chem. Soc.* **1959**, *81*, 6524.
(35) (a) Winstein, S. *Q. Rev. Chem. Soc.* **1969**, *23*, 141. (b) Warner, P. M. *Top. Nonbenzenoid Aromat. Chem.* **1976**, 2. (c) Paquette, L. A. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 106.
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(37) Childs, R. F.; Mulholland, D. L.; Varadarjan, A.; Yeroushalmi, S. *J. Org. Chem.* **1983**, *48*, 1431.
(38) This tilting allows overlap mostly or only on one side of the ring. It introduces some degree of s character to the mainly π overlap.[39] An extreme example in which the sp^2 carbon framework is set up for predominantly (p–p)σ overlap is C_{16}-hexaquinacene.[36e]
(39) Paquette, L. A.; Wallis, T. G.; Kempe, T.; Christoph, G. G.; Springer, J. P.; Clardy, J. *J. Am. Chem. Soc.* **1977**, *99*, 6946.
(40) Krüger, C.; Roberts, P. J.; Tsay, Y.-H.; Koster, J. B. *J. Organomet. Chem.* **1974**, *79*, 69.
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(46) (a) Masamune, S.; Sakai, M.; Kemp-Jones, A. V.; Ona, H.; Venor, A.; Nakashima, T. *Angew. Chem., Int. Ed. Engl.* **1973**, *12*, 769. (b) Masamune, S.; Sakai, M.; Kemp-Jones, A. V.; Nakashima, T. *Can. J. Chem.* **1974**, *52*, 855. (c) Masamune, S.; Sakai, M.; Kemp-Jones, A. V. *Can. J. Chem.* **1974**, *52*, 858. (d) Coates, R. M.; Fretz, E. R. *J. Am. Chem. Soc.* **1975**, *97*, 2538.
(47) (a) Winstein, S.; Kaesz, H. D.; Kreiter, C. G.; Friedrich, E. C. *J. Am. Chem. Soc.* **1965**, *87*, 3267. (b) Winstein, S.; Kreiter, C. G.; Brauman, J. I. *J. Am. Chem. Soc.* **1966**, *88*, 2047. (c) Warner, P.; Harris, D. L.; Bradley, C. H.; Winstein, S. *Tetrahedron Lett.* **1970**, 4013. (d) Paquette, L. A.; Broadhurst, M. J.; Warner, P.; Olah, G. A.; Liang, G. *J. Am. Chem. Soc.* **1973**, *95*, 3386.
(48) (a) Schröder, G.; Prange, U.; Bowman, N. S.; Oth, J. F. M. *Tetrahedron Lett.* **1970**, 3251. (b) Roberts, M.; Hamberger, H.; Winstein, S. *J. Am. Chem. Soc.* **1970**, *92*, 6346. (c) Warner, P.; Winstein, S. *J. Am. Chem. Soc.* **1971**, *93*, 1284. (d) Ahlberg, P.; Harris, D. L.; Roberts, M.; Warner, P.; Seidl, P.; Sakai, M.; Cook, D.; Diaz, A.; Dirlam, J. P.; Hamberger, H.; Winstein, S. *J. Am. Chem. Soc.* **1972**, *94*, 7063.
(49) Hehre, W. J. *J. Am. Chem. Soc.* **1974**, *96*, 5207.
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(56) These calculations show that both mechanisms shield the endo proton but, surprisingly, also slightly shield the exo proton. In homotropylium the bridging CH_2 is located directly over the C_1 to C_7 average ring plane,[41] placing even the endo proton in the shielding region generated by the ring current. In smaller, 7- or 6-membered, homoaromatic rings the bridging sp^3 atom is much less elevated and its projection falls outside the base ring plane. Its endo and exo substituents are expected to lie respectively in the shielding and deshielding regions.
(57) (a) Rieke, R.; Ogliaruso, M.; McClung, R.; Winstein, S. *J. Am. Chem. Soc.* **1966**, *88*, 4729. (b) Katz, T. J.; Talcott, C. *J. Am. Chem. Soc.* **1966**, *88*, 4732. (c) Smentowski, F. J.; Owens, R. M.; Faubion, B. D. *J. Am. Chem. Soc.* **1968**, *90*, 1537. (d) Winstein, S.; Moshuk, G.; Rieke, R.; Ogliaruso, M. *J. Am. Chem. Soc.* **1973**, *95*, 2624.
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since been strongly challenged by the results both of experiment[65] and of theoretical calculations which conclude that such stabilization is not possible.[65b,66] More recently, however, the argument for homoaromaticity in anions has been reaffirmed, again with the support of experiment[67] and calculation.[68]

Homoaromaticity in monohomoconjugated neutral systems has usually been inferred from NMR data, for example from the differential shift of protons in a bridging methylene group.[35c] In systems of potentially higher homoaromaticity photoelectron spectroscopy, X-ray data, and p orbital overlap calculations have also been employed.[35c,36e] Paquette's group has looked at neutral trishomoconjugated systems in detail. In these, mutual tilting of the p atomic orbital pairs in each of the three double bonds generates considerable end to end (σ, as opposed to π) overlap between homo atoms. It has been established beyond dispute that such an arrangment of orbitals is destabilizing (C_{16}-hexaquinacene was a key molecule in this argument[36e]). While it is thus evident that trishomoaromaticity does not occur to any significant extent, the further generalization that neutral homoaromaticity can never be observed[36e,69,70] continues to be resisted by other workers.[71-73]

Given the range and sophistication of calculation and experiment by the protagonists on both sides of the question, it would seem that homoaromaticity is still to some extent a matter of definition, from the rigorous[55,74] to the very flexible.[75]

The 1,6-dihydrotetrazines are an extension of the more general class of boat-shaped seven-membered carbo- and heterocycles in which an sp^3 atom is flanked by a π electron framework of sp^2 atoms,[76] e.g., cycloheptatriene, and 4*H*-1,2-,[77-79] and 6*H*-1,4-diazepines.[77]

As potential candidates for neutral monohomoaromaticity, all of these compounds have in common some mutually contradictory properties. They contain conjugatively unsaturated systems in which the bonding is largely localized and whose ends are too far apart to be effectively bonded[4,7,80,81] (though calculations suggest that some orbital overlap may occur, as in, for example, cycloheptatriene[39]). These facts argue against homoaromaticity. Supporting it, on the other hand, are the shielded and deshielded resonances observed for protons either on the sp^3 atom[1,77,79] or, one bond removed from it, on an alkyl substituent.[6,78] The magnitudes of the shift differences between these protons can be impressive, e.g., 3–4 ppm in the methylene groups of 2,3-dimethyl-5,7-diphenyl-6*H*-1,4-diazepine[77] or the 1,6-dihydro-1,2,4,5-tetrazines **1**.[1]

In the C_6 alkyltetrazines described here abundant examples are provided of C_6 H and C_6 CH, each in both highly shielded and high deshielded locations, either in the room temperature spectra or in the spectra of frozen conformations. The low temperature spectrum of **1a**,[1] or the juxtaposed spectra of **6** and **9** in Figure 3, are striking visualizations of these shielding–deshielding effects. If they are not indicative of homoaromaticity they must await some other explanation.

Experimental Section

NMR spectra were recorded on a Bruker WP-80 or WH-400 spectrometer. They were run in $CDCl_3$ solutions, except for variable-temperature work when CD_2Cl_2 or CD_3COCD_3 was used. *J* values are reported in hertz. Mass spectra were obtained on a Varian MAT CH7 or VG7070 F spectrometer.

Column chromatography was carried out on a 20 × 2 cm column of silica gel (70-270 mesh, Merck). Elemental analyses were performed by Guelph Chemical Laboratories, Guelph, ON. Melting points are uncorrected.

X-ray Crystallographic Analysis. Crystal data are summarized in Table I (supplementary material). Intensity data were collected on a Syntex $P2_1$ diffractometer. A standard reflection was monitored after every 40 measurements. This was used to scale the data to a common level. Data were corrected for Lorentz and polarization effects but not absorption. Both structures were solved by direct methods (MULTAN80) and refined by full-matrix least-squares methods. Hydrogen atoms were located from difference Fourier syntheses after two cycles of anisotropic refinement. In the final cycles of refinement, empirical weighting schemes were employed to give constant error throughout the various magnitudes of F_{obsd}. Final difference Fouriers were featureless with maximum residuals located in the vicinity of the oxygen atom in each case. Scattering factors were taken from the compilations of the International Tables[82a] and, for hydrogen, the data of Stewart et al.[82b] Computer programs used have been described elsewhere.[83]

1-Alkyl-3,6-dimethyl-1,6-dihydro-1,2,4,5-tetrazines (5–12). Method A. To a solution of 3,6-dimethyl-1,6-dihydro-1,2,4,5-tetrazine[11] (**4**, 0.50 g) and the alkyl bromide or iodide (2 equiv) in acetone (50 mL) was added anhydrous K_2CO_3 (5 g), and the resulting suspension was stirred at room temperature for 12 h. The yellow solution obtained on filtration was evaporated, and the residue chromatographed on silica gel with methylene chloride. The alkylated tetrazine was rapidly eluted, while unreacted **4** was retained on the column. The oily tetrazine obtained on evapo-

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ration was rather unstable at room temperature but could be kept for days at −10 °C. Freshly prepared samples gave the expected parent peak in the mass spectrum. The shielded and deshielded absorptions at C_6 in the ^1H NMR spectrum served to characterize these compounds. The NMR data are given in Table II.

Method B. 3,6-Dimethyl-1,6-dihydro-1,2,4,5-tetrazine (**4**, 0.50 g, 4.5 mmol) was added to an aqueous solution solution (50 mL) in which lithium metal (31.2 mg, 4.5 mmol) had been dissolved. The deep yellow solution was evaporated to dryness under reduced pressure, and the resulting solid lithium salt was taken up in ethanol (50 mL). The alkyl iodide (2 equiv) and anhydrous K_2CO_3 (5 g) were added, and the mixture was stirred for 12 h and worked up as before.

Both methods failed to yield the 1-neopentyltetrazine using neopentyl bromide.

The hydroxymethyl compound **5**, mp 76–77 °C, was made by the method of Skorianetz and Kovats.[11]

1-Acyl-3,6-dimethyl-1,6-dihydro-1,2,4,5-tetrazines (14–19). A solution of 3,6-dimethyl-1,6-dihydro-1,2,4,5-tetrazine (500 mg) and pyridine (353 mg, 1 equiv, except in the preparation of **17** and **18** where catalytic amounts were used) in methylene chloride (50 mL) was cooled to 0 °C, and the acylating agent (the chloride, except in the preparation of **14** where acetic anhydride was used) (1 equiv) was added slowly. After 30 min at room temperature the solution was extracted 3 times with water and then dried and evaporated. Unless the residue crystallized directly it was chromatographed with methylene chloride on silica gel and subjected to MS analysis to give the confirmatory parent peak. ^1H NMR data and elemental analyses are given in Table III.

1-Formyl-3,6-dimethyl-1,6-dihydro-1,2,4,5-tetrazine (13). Formic acid (98%, 1 mL) was added with cooling to acetic anhydride (2 mL). The mixture was heated to 50 °C and then cooled in ice.[84] The tetrazine **4** (500 mg) was added, and after 15 min the solution was evaporated and the residue chromatographed.

3,6-Diethyl-1,6-dihydro-1,2,4,5-tetrazine (27). This was prepared by the method of Skorianetz and Kovats,[23] and had mp 43–44 °C: δ ($CDCl_3$) 1.25 (C_6 CH_2*Me*, t, J = 7.8), 1.31 (C_3 CH_2*Me*, t, J = 7.8), 1.98 (C_6 H, t, J = 5.8), 2.30 (C_6 CH_2, m), 2.85 (C_3 CH_2, q), 6.6 (NH, broad); see Figure 4.

1-Acetyl-3,6-diethyl-1,6-dihydro-1,2,4,5-tetrazine (28). This compound was prepared as for the other acyl derivatives, but using acetyl chloride: δ ($CDCl_3$) 0.94 (C_6 CH_2*Me*, t, J = 8.1), 1.21 (C_6 C*H*Me, m), 1.31 (C_3 CH_2*Me*, t, J = 8.1), 1.55 (C_6 C*H*Me, m), 2.38 (COMe, s), 2.92 (C_3 C*H*$_2$Me), 6.64 (C_6 H, dd); see Figure 4.

3,6-Diisopropyl-1,6-dihydro-1,2,4,5-tetrazine (29). Isobutyraldehyde (50 g, 0.69 mol) and hydrazine (22.2 g, 0.69 mol) were refluxed in benzene (500 mL) using a Dean–Stark apparatus. When removal of water was complete, the benzene was evaporated and the residual oil distilled to give isobutyraldehyde hydrazone, which was stored at −10 °C. After 3 days a small amount of colorless crystals of 3,6-diisopropylhexahydro-1,2,4,5-tetrazine had separated out and these were collected and washed with cold ether. They were not stable at room temperature and were used immediately: δ ($CDCl_3$) 0.98 (C_3, C_6 CH*Me*$_2$, d, J = 6.5), 1.52 (C_3, C_6 C*H*Me$_2$, m), 2.79 (N_1, N_2, N_4, N_5-H, b), 3.40 (C_3, C_6 H, d, J = 6.1); peaks due to isobutyraldehyde hydrazone as a minor contaminant were also observed. The mother liquor from the original filtration, on keeping at −10 °C, slowly deposited further crops of crystals.

The hexahydro compound was dissolved in 3% aqueous NaOH and O_2 was bubbled through the solution for 16 h.[23] Saturation with ammonium chloride and repeated extraction with methylene chloride gave **29** as a pale yellow oil: δ ($CDCl_3$) 1.13 (C_6 CH*Me*$_2$, d, J = 6.4), 1.29 (C_3 CH*Me*$_2$, d, J = 6.8), 1.71 (C_6 H, d, J = 6.6), 2.53 (C_6 C*H*Me$_2$, m), 3.19 (C_3 *CH*Me$_2$, m), 5.59 (NH, b).

1,3,6-Triisopropyl-1,6-dihydro-1,2,4,5-tetrazine (30). The above oil was treated with isopropyl iodide in acetone in the presence of K_2CO_3 as described earlier (method A). The oily triisopropyl derivative **30** had δ (CD_3COCD_3, 400 MHz, 25 °C) 1.00, 1.07, 1.12, 1.17, 1.230, 1.233 (6 Me doublets), 1.73 (C_6 C*H*Me$_2$, m), 3.07 (C_3 C*H*Me$_2$, m; cf. compound **29**), 3.65 (NC*H*Me$_2$, m; cf. compound **8**), 3.87 (C_6 H, slightly broadened doublet); δ (−110 °C; two frozen conformations) 0.63, 0.86, 0.95, 1.00, 1.10, 1.16, 1.28, 1.48, 1.54 (9 Me doublets), 1.22 (3 Me doublets of almost identical shift), 2.53 (C_6 H endo, broad), 3.03, 3.13 (C_3 C*H*Me$_2$ for each conformation, multiplets), 3.66 (NC*H*Me$_2$ for both conformations), 5.40 (C_6 H exo, d); C_6 C*H*Me$_2$ obscured by Me region; see Figure 5 for some of the variable temperature spectra (supplementary material).

1-Acetyl-3,6-diisopropyl-1,6-dihydro-1,2,4,5-tetrazine (31). This was prepared as an oil from **29** using acetyl chloride and pyridine as described for the acyl derivatives in general. It had δ ($CDCl_3$) 0.83, 1.13 (C_6 CH*Me*$_2$, two d), 1.33 (C_3 CH*Me*$_2$, d), 1.55 (C_6 C*H*Me$_2$, m), 2.38 (COMe, s), 3.26 (C_3 C*H*Me$_2$, m), 6.38 (C_6 H, d, J = 9.6).

1-Acetyl-3-methyl-1,6-dihydro-1,2,4,5-tetrazine (32). 3-Methyl-1,6-dihydro-1,2,4,5-tetrazine (**1d**) was synthesized by the method of van der Plas[1] and converted with acetyl chloride and pyridine into **32**: δ ($CDCl_3$) 2.37 (COMe, s), 2.59 (C_3 Me, s), 4.74 (CH_2, s); in CD_2Cl_2 the three singlets showed no change down to −100 °C (80 MHz).

^{13}C NMR Spectroscopy. (a) The 3-Pentyl Derivative 10. δ ($CDCl_3$) at 35 °C included 150.3 (C_3); δ ($CDCl_3$–CH_2Cl_2) at −80 °C, 150.4, 151.1 (C_3, relative intensities ca. 1:2).

(b) The Benzhydryl Derivative 12. δ ($CDCl_3$) at 20 °C included 12.3 (C_6 *C*H$_3$), 17.6 (C_3 *C*H$_3$), 67.6, 72.3 (*C*HCH$_3$/*C*HPh$_2$), 138.8 (*o*-*C*), all sharp; δ ($CDCl_3$–CH_2Cl_2) at −100 °C, 14.9 (C_6 *C*H$_3$, broad), 17.9 (C_3 *C*H$_3$, sharp), 64.6, 74.6 (*C*HCH$_3$/*C*HPh$_2$, broad), 138.2, 139.0 (*o*-C, both sharp, comparable intensities).

(c) The Hydroxymethyl Derivative 5. δ ($CDCl_3$): 13.0 (C_6 *C*H$_3$), 17.1 (C_3 *C*H$_3$), 71.6 (C_6), 74.5 (CH_2), 150.4 (C_3) (all confirmed by off resonance decoupling); δ (solid, magic angle spinning) 13 (C_6 *C*H$_3$), 17 (C_3 *C*H$_3$), 74 (C_6 and CH_2), 150 (C_3).

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Registry No. **4**, 13717-81-2; **5**, 37454-62-9; **6**, 37454-61-8; **7**, 100928-48-1; **8**, 100928-49-2; **9**, 100928-50-5; **10**, 100928-51-6; **11**, 100928-52-7; **12**, 100928-53-8; **13**, 100928-54-9; **14**, 100928-47-0; **15**, 100928-55-0; **16**, 100928-56-1; **17**, 100928-57-2; **18**, 100928-58-3; **19**, 100928-59-4; **27**, 13717-87-8; **28**, 100928-60-7; **29**, 13717-89-0; **30**, 100928-61-8; **31**, 100928-62-9; **32**, 100928-63-0.

Supplementary Material Available: Crystallographic data for **5** and **14**, bond lengths, bond angles, and some intramolecular contacts of interest in compounds **5** and **14**, atomic coordinates and isotropic thermal parameters for compounds **5** and **14**, and 400-MHz variable-temperature ^1H NMR spectrum of compound **30** (5 pages). Ordering information is given on any current masthead page.

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