Conformational Dynamics of the Bent 1,5,2,4,6,8-Dithiatetrazocines

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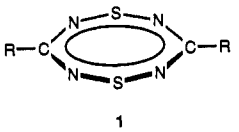
Abstract: 3,7-Bis(butylmethylamino)-1,5,2,4,6,8-dithiatetrazocine (**3**) was prepared in two steps from *N*-methylbutylamine in 14% overall yield. At room temperature the ^{1}H NMR spectrum of **3** shows two methyl resonances (in a roughly 1:1 ratio) and four resonances for the C$^\alpha$ methylene protons of the butyl groups (roughly 1:1:1:1). These data indicate that compound **3** displays both *cis/trans* isomerism and a bent heterocyclic ring in solution. Heating of compound **3** in a variable-temperature NMR experiment results in coalescence of the two methyl and four C$^\alpha$ resonances to a singlet and a triplet, respectively, at temperatures corresponding to an activation energy ($\Delta G_c^\ddagger$) of approximately 17 kcal/mol for the exchange process. This value is the free energy of activation for rotation of the dialkylamino groups and also represents a lower limit for the activation energy for inversion of the bent dithiatetrazocine ring. *Ab initio* calculations on the 3,7-diamino-1,5,2,4,6,8-dithiatetrazocine system suggest that the activation energies for amine rotation and ring inversion are very similar: 17.1 and 17.3 kcal/mol, respectively. Spectral simulations of the NMR data for **3** support this conclusion, with the best experimental estimates of the free energies of activation for the two processes being 17.3 ± 0.1 and 17.7 ± 0.5 kcal/mol, respectively. Notably, the calculations indicate that the ring inversion procedes asymmetrically—in the transition state one side of the ring is more highly bent than the other—and there is a nearly planar intermediate along the pathway.

The 1,5,2,4,6,8-dithiatetrazocines, first reported from the Woodward group in 1981,[1] exhibit a remarkable structural dichotomy.[2] In derivatives where the R groups are aryl,[1] *tert*-butyl,[3] furyl, or thienyl,[4] the heterocycle is planar[1] and easily understood as a 10 π-electron aromatic system (**1**). However, where both[1] or one[4] of the R groups is a dimethylamino group, the heterocycle is sharply folded (e.g., **2**), with a dihedral angle of 105.7° in the one crystallographically characterized example.[1] Do these curiously bent aromatic systems reflect shallow minima in a complex potential energy surface, or are they sufficiently rigid to form the basis for an unusual class of stereoisomers? We report herein the results of NMR and computational studies which elucidate the conformational behavior of the amino-substituted 1,5,2,4,6,8-dithiatetrazocines.



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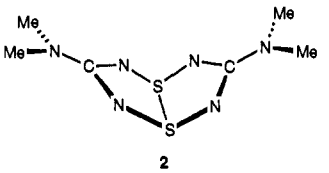

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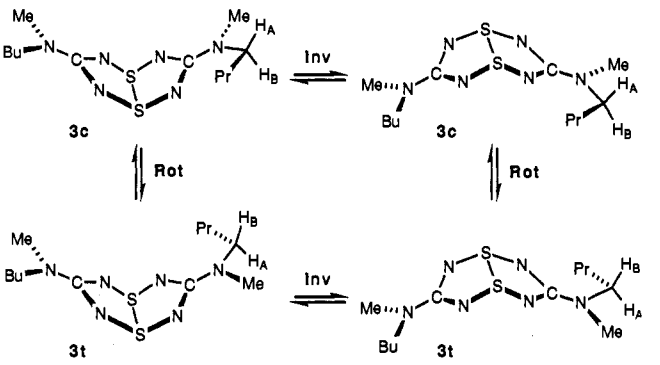
Results and Discussion

NMR Experiments. Experimental studies of the conformational dynamics of the bent dithiatetrazocines require a less symmetric derivative than the previously known examples. For this purpose we prepared 3,7-bis(butylmethylamino)-1,5,2,4,6,8-dithiatetrazocine (**3**) by a method entirely analogous to that used for the synthesis of **2**.[1] Two dynamic processes are likely for the dithiatetrazocines, amine rotation (Rot) and ring inversion (Inv), and their relative rates determine which effects on the spectroscopic properties of compound **3** may be observable. If amine rotation is slow, then *cis/trans* isomerism will be found, regardless of the rate of ring inversion. If both rotation and inversion are slow, then the methylene protons of both the *cis* (**3c**) and *trans* (**3t**) isomers will be diastereotopic. Note that the *trans* isomer is chiral, but the *cis* isomers is not, so if both processes are slow, a chiral shift reagent or chiral solvent may distinguish the *trans* enantiomers. Difficulties arise only if amine rotation is fast; in this circumstance the rate of ring inversion in **3** has no spectroscopic consequences.

Scheme 1



The 500-MHz ^{1}H NMR spectrum of compound **3** (Figure 1) at room temperature shows two *N*-methyl resonances (δ 2.76 and 2.78; in a roughly 1:1 ratio), clearly indicating that **3** exists as mixture of *cis* and *trans* isomers. In addition, there are four resonances (δ 3.00, 3.11, 3.42, and 3.49; roughly 1:1:1:1) corresponding to two pairs (*cis* and *trans*) of diastereotopic C$^\alpha$ methylene protons on the butyl groups, and this multiplicity can arise only if the dithiatetrazocine ring is bent and noninverting on the NMR time scale.[5] The *cis* and *trans* isomers of **3** were further characterized by recording the ^{1}H NMR spectrum in a chiral solvent. In 1:2 *d*-phenyltrifluoromethylcarbinol/toluene-d_8 the upfield methyl resonance of **3** was split by 1.3 Hz (Figure

* Abstract published in *Advance ACS Abstracts,* May 15, 1994.

(1) Ernest, I.; Holick, W.; Rihs, G.; Schomberg, D.; Shoham, G.; Wenkert, D.; Woodward, R. B. *J. Am. Chem. Soc.* **1981**, *103*, 1540–1544.

(2) For a review of experimental and theoretical studies of the heterocyclic thiazenes, see: Oakley, R. T. *Prog. Inorg. Chem.* **1988**, *36*, 299–391.

(3) Gleiter, R.; Bartetzko, R.; Cremer, D. *J. Am. Chem. Soc.* **1984**, *106*, 3437–3442.

(4) Amin, M.; Rees, C. W. *J. Chem. Soc. Perkin Trans. 1* **1989**, 2495–2501.

(5) Unfortunately, in the ^{13}C NMR spectrum (67.9 MHz, $CDCl_3$) of compound **4**, the *cis/trans* isomerism is only evident in a slight broadening of the C$^\alpha$ (δ 50.9) and methyl (δ 36.5) resonances.

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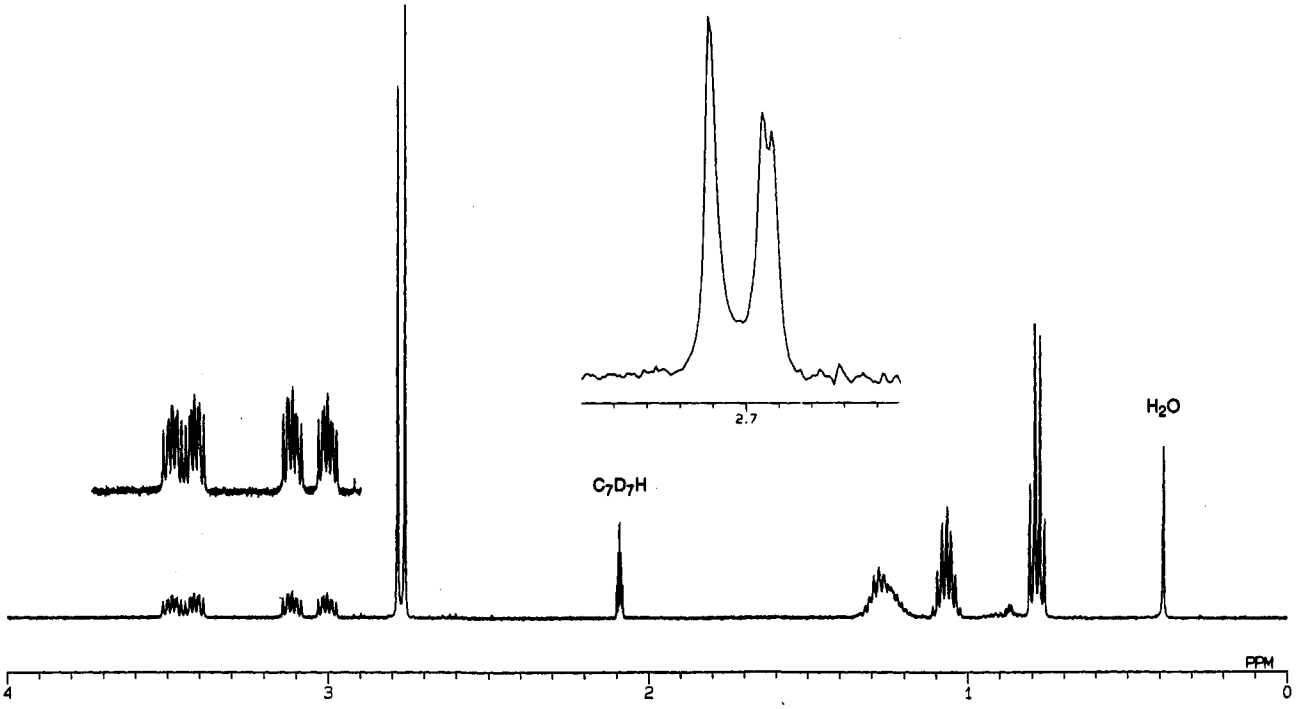

Figure 1. ^{1}H NMR spectrum (500 MHz, toluene-d_8, 20 °C) of compound **3**. The inset is an expansion of the methyl resonance region of a similar spectrum recorded in the chiral solvent mixture 1:2 *d*-phenyltrifluoromethylcarbinol/toluene-d_8.

1, insert), clearly assigning this resonance to the chiral *trans* isomer (**3t**). Naturally, the achiral *cis* isomer was unaffected by the chiral solvent. Chiral shift reagents were also employed for NMR studies, but no useful separations of resonances were obtained. In view of the low basicity of the dithiatetrazocines,[1] they may be expected to coordinate only very weakly with these reagents. From the difference in intensities of the *cis* and *trans* methyl resonances, it is possible to assign the methylene resonances at δ 3.00 and 3.49 to the *cis* isomer and those at δ 3.11 and 3.42 to the *trans*.

If the activation energy for amine rotation is great enough, then *cis*/*trans* isomers should be isolable; however, both liquid and gas chromatography showed only a single component for compound **3**. This suggests that the barrier is relatively modest and that dynamic NMR experiments should yield the activation energy. In such a variable-temperature NMR experiment, if the inversion process is significantly faster than amine rotation, then the four C^α multiplets should first coalesce to two triplets (*cis* and *trans* remain), and further heating would result in coalescence of the pairs of C^α triplets and *N*-methyl singlets to one triplet and one singlet, respectively, as amine rotation becomes fast. If, however, amine rotation is as fast or faster than inversion, then the C^α multiplets and *N*-methyl singlets should coalesce to a triplet and a singlet in a uniform process. In the actual experiment (Figure 2), the latter result was obtained, with ΔG_c^* for methyl coalescence estimated to be 17.3 ± 0.1 kcal/mol. This figure represents the free energy of activation for rotation of the dialkylamino groups about the exocyclic C–N bond, but it *also* represents a lower limit for the activation energy for inversion of the bent dithiatetrazocine ring.

Computational Studies. The initial analysis of the NMR experiments only placed a lower limit on the value of the activation energy for ring inversion, so *ab initio* molecular orbital calculations were employed to investigate this process.[6] In order to keep the calculations to a manageable size, we examined the energies of various conformations of the parent compound, 3,7-diamino-1,5,2,4,6,8-dithiatetrazocine, rather than the bis(dialkylamino) derivative which was employed in the experimental studies. The results of these calculations are summarized in Table 1 and Figure 3.

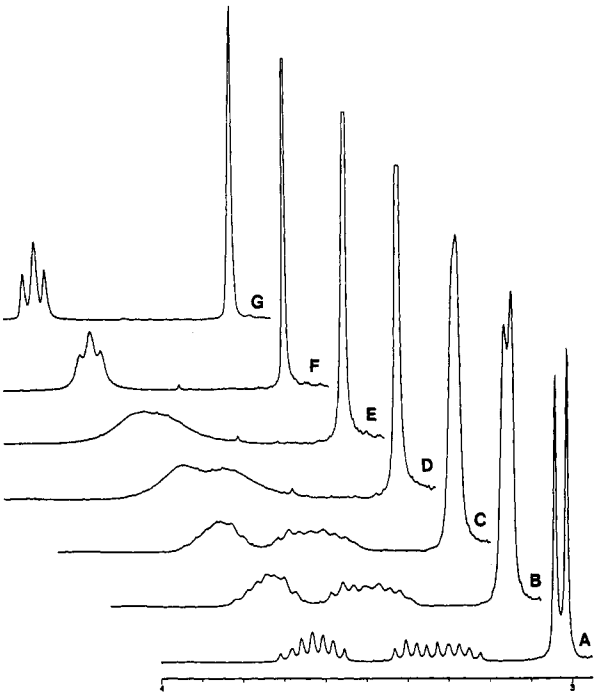

Figure 2. ^{1}H NMR spectra (270 MHz, chlorobenzene-d_5) of compound **3** recorded at various temperatures. Only the δ 3–4 region is shown. The spectra were recorded at 24 (spectrum A), 41 (B), 44 (C), 64 (D), 69 (E), 91 (F), and 120 °C (G). Additional details are given in the Experimental Section.

In order to calibrate the computational results, the barrier to amine rotation was evaluated first. The HF/3-21G(*) computational level[7] was the lowest to give a reasonable equilibrium structure (**4**) for diaminodithiatetrazocine. The fully optimized

(6) Previously reported *ab initio* molecular orbital calculations on the 1,5,2,4,6,8-dithiatetrazocines have focused on the electronic structure of these molecules and their planar/folded structural dichotomy but have not addressed the issue of conformational dynamics: (a) Millefiori, S.; Millefiori, A.; Granozzi, G. *Inorg. Chim. Acta* **1984**, *90*, L55–L58. (b) Boutique, J. P.; Riga, J.; Verbist, J. J.; Delhalle, J.; Fripiat, J. G.; Haddon, R. C.; Kaplan, M. L. *J. Am. Chem. Soc.* **1984**, *106*, 312–318. (c) Gleiter, R.; Bartetzko, R.; Cremer, D. *J. Am. Chem. Soc.* **1984**, *106*, 3437–3442.

Table 1. Computational Data[a] for Various Conformations of 3,7-Diamino-1,5,2,4,6,8-dithiatetrazocine

conformer	computational level	symmetry	energy[b] (au)	no. of imaginary freq	S–S distance (Å)	ring fold angle[c] (deg)
4	HF/3-21G(*)	C_{2v}	−1193.704 567	0	2.502	107.8
	HF/6-31G*	C_{2v}	−1199.648 977	0	2.281	107.9
	exptl (for **2**)[d]				2.428	105.7
5	HF/3-21G(*)	C_1	−1193.667 783	1	2.518	109.0
	HF/6-31G*	C_1	−1199.621 728	1	2.267	108.5
6	HF/6-31G*	C_{2v}	−1199.616 833	2	3.420	127.9
7	HF/6-31G*	C_s	−1199.621 339	1	3.610	131.3
8	HF/6-31G*	C_s	−1199.626 374	0	3.859	174.7

[a] See the Experimental Section for computational details. [b] 1 au = 627.503 kcal/mol. [c] The ring fold angle is defined to be the angle formed by the two ring carbon atoms and the midpoint between the two ring sulfur atoms. [d] Data from ref 1.

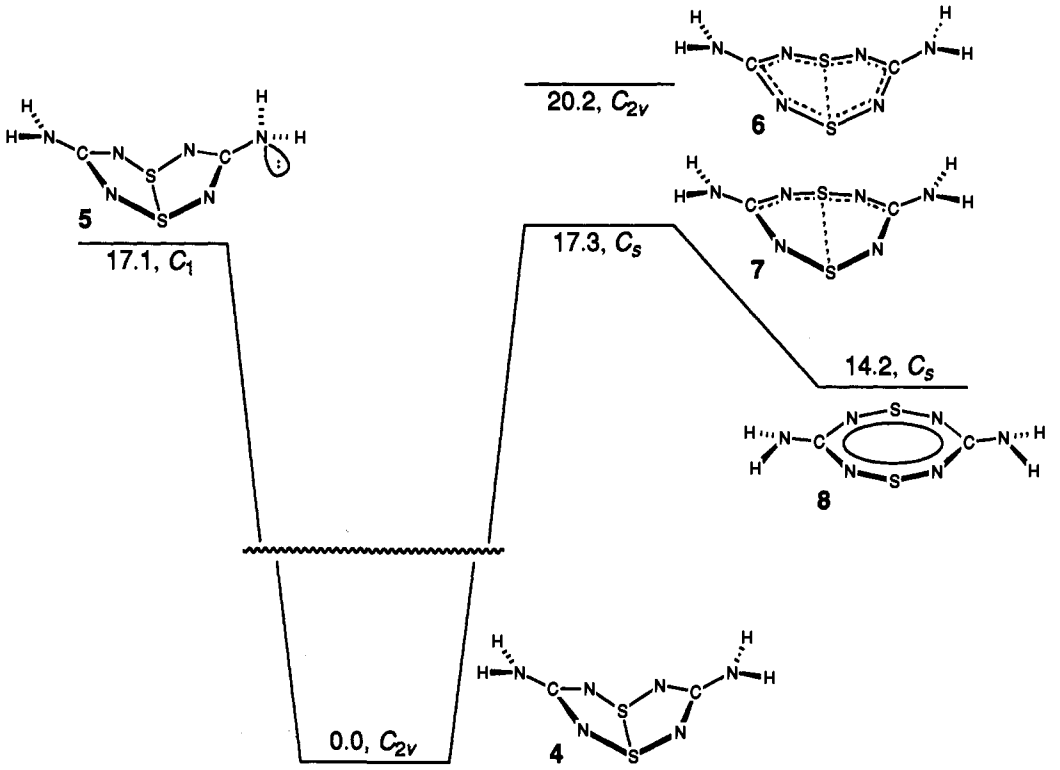

Figure 3. Potential energy diagram illustrating the calculated (HF/6-31G*) relative energies of various ground-state, intermediate, and transition-state structures of 3,7-diamino-1,5,2,4,6,8-dithiatetrazocine involved in amine rotation and ring inversion. (See also Table 1) The information just above or below each plateau indicates the energy (in kcal/mol relative to the ground state **4**) and symmetry of the illustrated conformation.

geometry possesses C_{2v} symmetry, and the calculated S–S distance of 2.502 Å and the fold angle of 107.8° (see Table 1) are in fair agreement with the experimental values of 2.428 Å and 105.7° from the X-ray structure of compound **2**.[1] The transition state for the rotation of a single amino group (**5**) was then located, and its energy was calculated to be 23.1 kcal/mol higher than the ground state, but from the NMR data we knew this value to be in error by some 6 kcal/mol. This series of calculations was repeated at the HF/6-31G* level, and the situation was much improved: the calculated activation energy of 17.1 kcal/mol for amine rotation (see Figure 3) is in excellent agreement with the NMR data. Interestingly, the calculated S–S distance for **4** at this level is only 2.281 Å, significantly less than the experimental value for **2**. The HF/6-31G* amine rotation transition-state structure (**5**) is illustrated in Figure 4. The amino group undergoing rotation is much more highly pyramidalized than the nearly planar amines of **4**, but the dithiatetrazocine ring geometries in **4** and **5** are essentially identical.

The HF/6-31G* level was employed for all calculations related to the ring inversion process. The transition state was sought initially by systematically varying the S–S distance with optimization of all other parameters under the constraint of C_{2v} symmetry. A stationary point was found at an S–S distance of 3.420 Å (**6**) which was 20.2 kcal/mol above the ground state, but a frequency calculation yielded two imaginary frequencies for this structure. The same search procedure was then followed with a lowered symmetry constraint, and the true ring inversion transition state (**7**) was soon located. Structure **7** has C_s symmetry and is illustrated in Figure 4; the S–S distance is 3.610 Å, and the fold angle is approximately 131.3°. The structure resembles a rather bowed dithiatetrazocine in which one sulfur atom has been strongly bent out of the mean plane of the heterocycle. The activation energy for ring inversion is calculated to be 17.3 kcal/mol, barely higher than the calculated barrier to amine rotation.

Inasmuch as the fold angle of **7** does not approach 180°, there must be at least one intermediate along the ring inversion pathway. Further widening of the S–S distance leads to conformer **8**, a relatively flat, C_s symmetric intermediate which is 14.2 kcal/mol above the ground state. The two amines are slightly pyramidalized in this structure, and the inversion of one or both of the amino groups (processes with very small activation energies) will yield other intermediates of comparable energy, but this portion of the reaction coordinate was not explored in detail.

NMR Simulations. The computational studies suggested that the barriers to amine rotation and ring inversion are remarkably similar. Ring inversion can have no effect on the interconversion

(7) Hehre, W. J.; Radom, L.; Schleyer, P. v. R.; Pople, J. A. *Ab Initio Molecular Orbital Theory*; John Wiley & Sons: New York, 1986; pp 63–100.

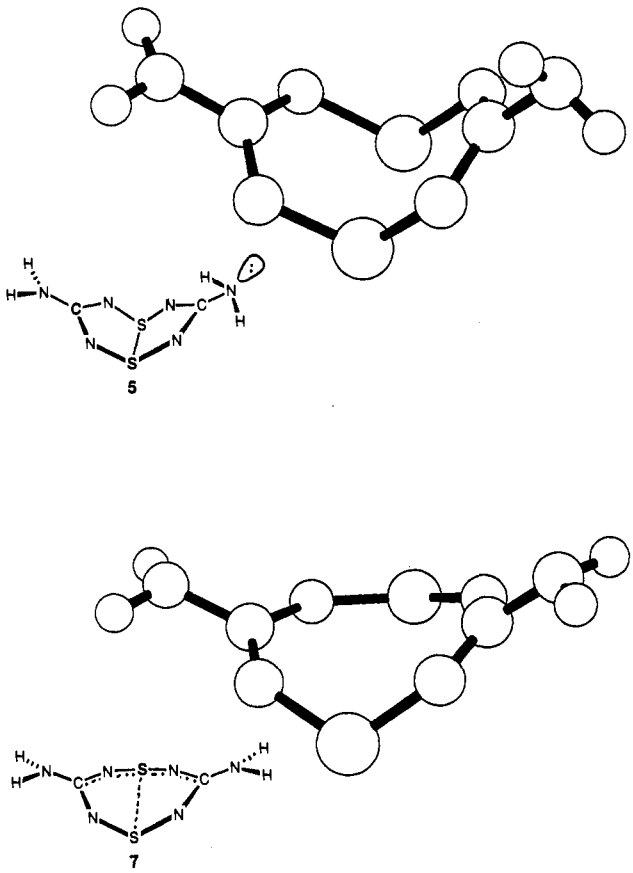

Figure 4. Perspective drawings of the calculated (HF/6-31G*) transition-state geometries for amine rotation (**5**, above) and ring inversion (**7**, below).

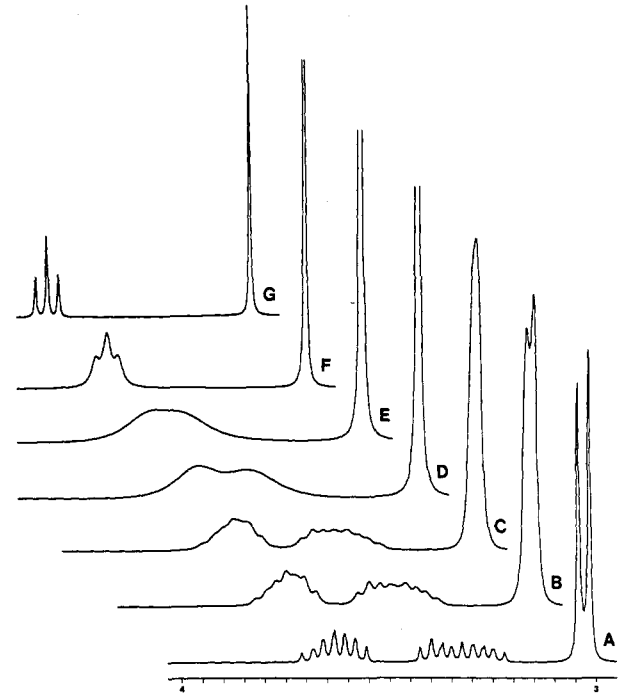

Figure 5. Simulated (DNMR6) ^{1}H NMR spectra of compound **3** corresponding to the spectra illustrated in the variable temperature NMR experiment of Figure 2. The rate constants employed in the simulations were the following: spectrum A, k_{rot} = 1.3, k_{inv} = 0.65 s^{-1}; B, 6, 3 s^{-1}; C, 8, 4 s^{-1}; D, 52, 26 s^{-1}; E, 74, 37 s^{-1}; F, 336, 168 s^{-1}; G, 1860, 930 s^{-1}. Additional details are given in the Experimental Section.

of the *cis* and *trans* isomers of **3**, but this process should affect the appearance of the methylene resonances as they undergo coalescence. Accordingly, the program DNMR6[8] was employed to simulate the seven spectra of compound **3** illustrated in Figure 2. These simulations explicitly included rate constants for all amine rotation and ring inversion processes, and the results of the simulations are illustrated in Figure 5. Particular attention was paid to the spectra recorded near methyl coalescence (spectra B and C in both Figures 2 and 5), and in order to obtain reasonable simulations of these spectra it proved necessary to include ring inversion rate constants comparable in magnitude to the rate constants for amine rotation. The best fits were obtained when the ring inversion rate constants (k_{inv}) were set to half the value of the amine rotation rate constants (k_{rot}). Thus at methyl coalescence (44 °C, the spectra C in Figures 2 and 5), k_{rot} = 8 s^{-1} and k_{inv} = 4 s^{-1}, corresponding to free energies of activation of $\Delta G_{rot}^{\ddagger}$ = 17.3 kcal/mol and $\Delta G_{inv}^{\ddagger}$ = 17.7 kcal/mol, in good agreement with the computational results.

The sensitivity of the simulations to small variations in k_{rot} and k_{inv} is illustrated by the matrix of spectra in Figure 6, which are attempts to simulate the experimental spectrum recorded at 41 °C (Figure 2, spectrum B). By comparison of the spectra, it is seen that the methyl line shapes are sensitive only to the magnitude of k_{rot}, as expected, but the methylene line shapes are sensitive to both k_{rot} and k_{inv}. The center spectrum is the best fit, and it is the one shown in Figure 5 (spectrum B), but the differences are relatively subtle. An even better fit may be obtained if one assumes that the rates of ring inversion of the *cis* and *trans* isomers are different, but in our opinion there is insufficient experimental data to warrant the inclusion of this extra variable. From analysis of these and other spectra, it is clear that the barrier to amine rotation is significantly better determined than that for ring inversion; a reasonable estimate of the error in $\Delta G_{rot}^{\ddagger}$ is ±0.1 kcal/mol, but that for $\Delta G_{inv}^{\ddagger}$ is ±0.5 kcal/mol or greater.

In conclusion, the bent dithiatetrazocines exhibit both *cis*/*trans* and ring inversion isomerism on the NMR time scale. The activation energies for amine rotation and ring inversion are coincidentally very similar but are too low to permit the isolation of stereoisomers at room temperature. Interestingly, in the related 1,5-diphosphadithiatetrazocines, which have tetracoordinate phosphorus in place of trigonal carbons, ring inversion is slow, so that geometric isomers related by ring inversion may be isolated and characterized.[9]

Experimental Section

3,7-Bis(butylmethylamino)-1,5,2,4,6,8-dithiatetrazocine (3). 2-Ethyl-2-thiopseudourea hydrobromide (5.37 g, 29 mmol) and *N*-methylbutylamine (2.88 g, 33 mmol) were heated overnight at 80 °C in water (40 mL). The solvent was evaporated, and any residual water was removed with a toluene–ethanol azeotrope to leave crude *N*-methyl-*N*-butylguanidine hydrobromide as a colorless syrup. A portion of this material (5.56 g, 26.5 mmol) and DBU (16.1 g, 106 mmol) were mixed in methylene chloride (100 mL) and cooled to 5 °C. Sulfur dichloride (2.54 mL, ~40 mmol) was added dropwise over two minutes, and the solution turned dark red almost immediately. After stirring overnight at room temperature, the solution was washed three times with water. The organic layer was dried over sodium sulfate and concentrated. Purification by silica gel column chromatography (solvent, 20:1 toluene–ethyl acetate) gave compound **3** as a golden yellow oil (580 mg) which solidified in the refrigerator; mp 49–51 °C; ^{1}H NMR (500 MHz, toluene-d_8, 20 °C) δ 0.78 (t, 3H, *J* = 7 Hz), 0.79 (t, 3H, *J* = 7 Hz), 1.07 (m, 4H), 1.26 (m, 4H), 2.76 (s, 3H), 2.78 (s, 3H), 3.00 (ddd, 1H, *J* = 13, 8, 6 Hz), 3.11 (ddd, 1H, *J* = 13, 8, 6 Hz), 3.42 (ddd, 1H, *J* = 13, 8, 6 Hz), 3.49 (ddd, 1H, *J* = 13, 8, 6 Hz); ^{1}H NMR (270 MHz, nitrobenzene-d_5, 120 °C) δ 0.87 (t, 6H, *J* = 7 Hz), 1.24 (sextet, 4H, *J* = 7 Hz), 1.52 (quintet, 4H, *J* = 7 Hz), 3.08 (s, 6H), 3.53 (t, 4H, *J* = 7 Hz); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 13.4, 19.4, 29.0, 36.5, 50.9, 179.3; MS, *m/z* 316 (M^+, 50), 273

(8) Brown, J. H.; Bushweller, C. H. *DNMR6: Calculation of NMR Spectra (I = 1/2) Subject to the Effects of Chemical Exchange*; QCPE Program No. 633.

(9) Chivers, T.; Edwards, M.; Parvez, M. *Inorg. Chem.* **1992**, *31*, 1861–1865.

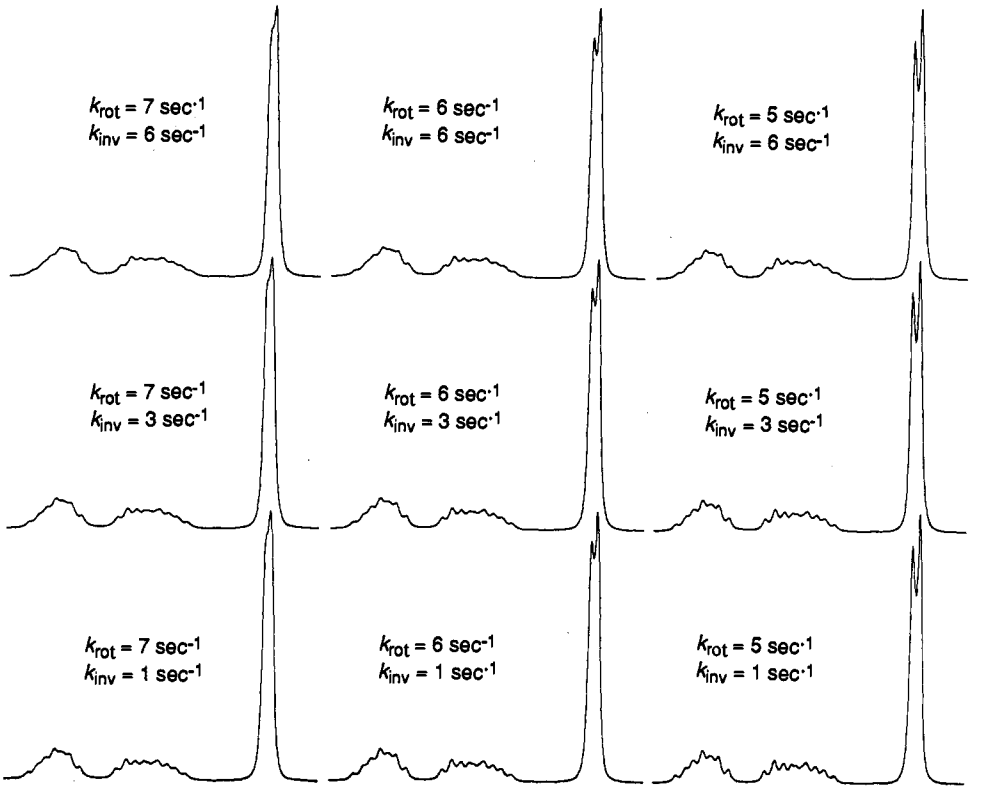

Figure 6. Sensitivity of the simulations (DNMR6) of the ^{1}H NMR spectrum of compound **3** (41 °C, Figure 2, spectrum **B**) to the choice of rate constants for amine rotation and ring inversion. See the text for discussion.

(M – C_3H_7, 3), 190 (M – $N_2CNMeBu$, 100); exact mass 316.1501, calcd for $C_{12}H_{24}N_6S_2$ 316.1504. This material showed a single component on silica gel TLC (solvent, 4:1 toluene–ethyl acetate; R_f 0.79), and it was estimated to be 99% pure by capillary column GC (Supelco SPB-1, 30 m × 0.53 mm; temperature program 120–280 °C).

Variable-Temperature NMR Experiments. Compound **3** was dissolved in chlorobenzene-d_5, and 270 MHz ^{1}H NMR spectra were recorded at a variety of temperatures from 24 to 120 °C (see Figure 2). Temperatures were measured by means of a thermocouple mounted in the NMR spectrometer probe, and the sample was allowed to equilibrate at each of the chosen temperatures for 10 min prior to the recording of the spectrum. Spectra were recorded at increments of 1–3 K near the coalescence temperatures. For the methyl singlets, the peak separation in the absence of exchange ($\Delta\nu$) was 7.6 Hz, while the diastereotopic C$^\alpha$ proton resonances appear as two complex multiplets separated by 82 Hz. Coalescence of the methyl resonances was observed at 317 ± 1 K (44 °C). By using the Gutowsky–Holm approximation[10] the apparent value of k_c was calculated 16.88 s^{-1}; however, because there are two independent amine groups which may undergo rotation, the rate constant for each amine rotation (k_{rot}) must be 8.44 s^{-1}. A transmission coefficient of 1 was assumed for the Eyring equation, and thus $\Delta G_{rot}^{\ddagger}$ is 17.3 ± 0.1 kcal/mol.[10] Coalescence of the C$^\alpha$ methylene resonances was observed at 343 ± 2 K (70 °C). Ignoring contributions from ring inversion and spin–spin coupling, this yields values of k_c = 182.2 s^{-1}, k_{rot} = 91.1 s^{-1}, and $\Delta G_{rot}^{\ddagger}$ = 17.1 kcal/mol. Essentially identical results were obtained from experiments in toluene-d_8 at 500 MHz: for methyl coalescence, $\Delta\nu$ = 11.4 Hz; T_c = 322 ± 1 K; k_c = 25.33 s^{-1}; k_{rot} = 12.67 s^{-1}; $\Delta G_{rot}^{\ddagger}$ = 17.3 ± 0.1 kcal/mol.

(10) Sandstrom, J. *Dynamic NMR Spectroscopy*; Academic: New York, 1982; pp 77–123.

Computational Studies. Geometries were fully optimized at the Hartree–Fock level of theory, in some cases under a constraint of symmetry or a selected bond distance or angle. All calculations were performed by using the SPARTAN 2.0 package of programs (Wavefunction, Inc.), and its built-in default thresholds for wave function and gradient convergence were employed. Frequency calculations were performed on all optimized equilibrium and transition-state geometries. The atomic coordinates for each of the calculated geometries in Table 1 are contained in the supplementary material.

NMR Simulations. Spectra were simulated by using the program DNMR6.[8] The values for chemical shifts and coupling constants in the absence of exchange were taken from a spectrum of **3** recorded in chlorobenzene-d_5 at 500 MHz at 20 °C. The ratio of *cis* and *trans* isomers was taken to be 48:52. For all lines, T_2 was taken to be 0.3 s. Coupling constants, T_2's, and the chemical shifts of the methyl resonances were held constant in all the simulated spectra. The four methylene resonance chemical shifts were allowed small, linear variations with temperature.[10] The rate constants for the various exchange processes used for each simulation are given in Figures 5 and 6.

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Supplementary Material Available: Listing of Cartesian coordinates of **4–8** (2 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.