Chemistry of *N*-Thiosulfinylanilines. III. Thiosulfinylamine—5*H*-1,2,3-Dithiazole Equilibrium as Studied by NMR Spectroscopy

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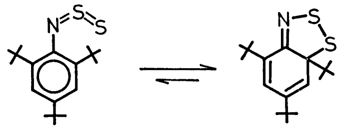
Thermodynamic parameters ($\Delta H=-4.9$ kcal mol^{-1}, $\Delta S=-11.3$ cal mol^{-1} deg^{-1}) were determined for cyclization of 2,4,6-tri-*t*-butyl-*N*-thiosulfinylaniline (**1b**) (the minor component) into 2,4,6-tri-*t*-butyl-7,8-dithia-9-azabicyclo[4.3.0]nona-2,4,9-triene (**1a**) (the major component) by means of NMR spectroscopy. Using these values, π-bond of thiosulfinylamino group (–N=S=S) was estimated to be weaker than that of sulfinylamino group (–N=S=O) by, at least, 25 kcal mol^{-1}. The equilibrium ratio [**1a**]/[**1b**] is subject to considerable solvent effect, polar solvents favoring the cyclic form (**1a**). Similarity of the thiosulfinylamine-dithiazole equilibrium to that of azidoimine-tetrazole has been pointed out.

In the previous papers,[1,2] we reported that 2,4,6-tri-*t*-butyl-*N*-thiosulfinylaniline (**1b**) is in equilibrium with a cyclized form, 2,4,6-tri-*t*-butyl-7,8-dithia-9-azabicyclo[4.3.0]nona-2,4,9-triene (**1a**) in solution, while in the solid state only **1a** exists. This is, to our knowledge, the first example where aromaticity of the benzene ring is destroyed during intramolecular 1,3-dipolar cyclization, although many examples of such a ring-chain isomerization are known for azidoimine-tetrazole systems.[3] We became interested in factors influencing the equilibrium between **1b** and **1a** and this paper describes the thermodynamic properties and solvent effects of this equilibrium.



1b **1a**

Experimental

The NMR spectra were recorded with a JEOL C60-HL spectrometer (60 MHz) equipped with a variable temperature apparatus. 2,4,6-Tri-*t*-butyl-7,8-dithia-9-azabicyclo[4.3.0]nona-2,4,9-triene (**1a**, mp 98.5—99.5 °C) was prepared as described previously.[2]

Results and Discussion

Temperature Effect. As interconversion between **1a** and **1b** was slow enough to show two sets of NMR signals due to the two tautomers (see Fig. 1), equilibrium constants were calculated based on NMR signal intensity of the two olefinic protons of **1a** and the two aromatic protons of **1b**. Table 1 shows the temperature dependence of the equilibrium constant and the free energy of isomerization measured in carbon tetrachloride solution (0.31 M) over a temperature range of 11—63 °C, where ΔG's correlate with temperatures linearly. Over the temperature range studied the major component was **1a** but the relative amount of **1b** increased with increasing temperature. Slight decomposition was observed above 60 °C. Based on the data in Table 1, the heat of isomerization (ΔH) and the entropy of isomerization (ΔS) were estimated to be -4.9 kcal mol^{-1} and -11.3 cal mol^{-1} deg^{-1}, respectively. These thermodynamic quantities bear a striking resemblance to those reported for the azidoimine–tetrazole equilibrium;[3] for instance, for the equilibrium between 2-azidopyrimidine (**2b**) and tetrazolo-

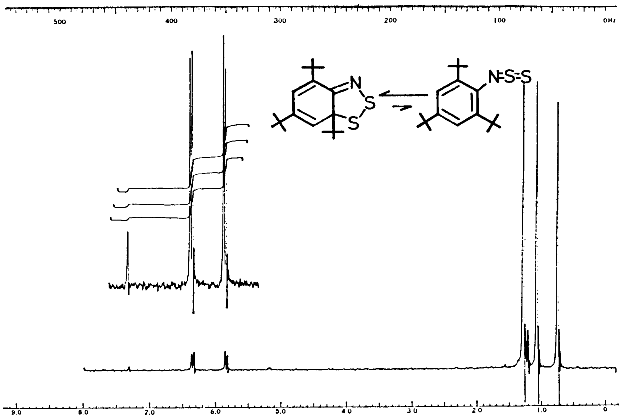


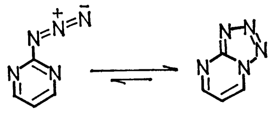
Fig. 1. NMR spectrum of an equilibribrium mixture **1a**+**1b** in CD_2Cl_2 (0.48 M) at 35 °C.

Table 1. Temperature dependence of K and ΔG in CCl_4

Temp (°C)	$K=\frac{[\mathbf{1a}]}{[\mathbf{1b}]}$	$-\Delta G$ (kcal mol^{-1})
11	19.5	1.68
23	14.1	1.56
30	12.0	1.50
33	10.7	1.44
38	9.9	1.42
43	9.2	1.39
48	8.2	1.34
52	6.6	1.22
58	5.7	1.14
63	5.1	1.09

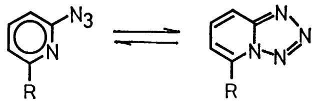
At lower temperatures (*e.g.* < 0 °C), linear correlation between T and ΔG did not hold because the equilibrium was reached much slower.

[1,5-*a*]pyrimidine, ΔH and ΔS have been reported to be -5.1 kcal mol^{-1} and -11.3 cal mol^{-1} deg^{-1}, respectively, in dimethyl sulfoxide-d_6.[4)]



2b **2a**

For equilibria **3b**⇄**3a** and **4b**⇄**4a**, ΔH's of -4.2 and -3.4 kcal mol^{-1} have been reported.[5)]

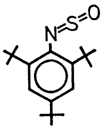


3 R=NO$_2$
4 R=Cl

3b, 4b **3a, 4a**

The similarity of these thermodynamic quantities, however, is somewhat surprising considering that the azidoimine–tetrazole reaction is a 6π-to-10π conversion without loss of aromaticity, at least in a formal sense, while the thiosulfinylamine–dithiazole reaction is accompanied by complete loss of aromaticity.

The exothermicity of this unusual ring formation of **1b** into **1a** may be attributable to both decreased aromaticity due to steric congestion by the three bulky groups ajacent to each other and high reactivity of the thiosulfinylamino group towards a double bond as demonstrated by 1,3-dipolar addition of *p*-dimethylamino-*N*-thiosulfinylaniline to olefins.[6)] Since 2,4,6-tri-*t*-butyl-*N*-sulfinylaniline (**5**)[2)] was found to have no tendency to isomerize into its cyclic form **5a**, steric congestion alone is not sufficient for ring formation. But the lack of aromaticity due to the steric congestion is an essential factor for cyclization because in the case of 2,4-di-*t*-butyl-6-methyl-*N*-thiosulfinylaniline (**6**) no evidence for the ring formation was obtained by NMR over a temperature range of -102—70 °C.



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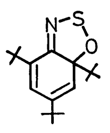
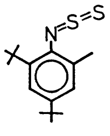


5a



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Difference between the π-bond energy of sulfinylamino group (–N=S=O) and that of thiosulfinylamino group (–N=S=S) can be roughly estimated using the thermodynamic data obtained above. Assuming that 1% (limit of detection) of 2,4,6-tri-*t*-butyl-*N*-sulfinylaniline (**5**) exists in its cyclic form **5a**, the free energy of isomerization of **5** into **5a** (ΔG^{NSO}) is calculated to be 2.79 kcal mol^{-1} (endothermic) at 33 °C. On the other hand, free energy of isomerization of **1b** into **1a** (ΔG^{NSS}) was -1.44 kcal mol^{-1} (exothermic) at 33 °C. If we assume that entropy changes in both isomerizations are equal and that σ bond energies of the N–S, S–O, and S–S bonds do not change through isomerization, the following equation can be given,

$$\begin{aligned}\Delta\Delta G &= \Delta G^{\mathrm{NSO}} - \Delta G^{\mathrm{NSS}} = \Delta H^{\mathrm{NSO}} - \Delta H^{\mathrm{NSS}}\\ &= (\sigma^{\mathrm{CO}} - \pi^{\mathrm{NSO}}) - (\sigma^{\mathrm{CS}} - \pi^{\mathrm{NSS}})\\ &= 4.23\ \text{kcal mol}^{-1},\end{aligned}$$

where σ^{CO} is C–O single bond energy to be gained on cyclization of **5**, σ^{CS} is C–S single bond energy to be gained on cyclization of **1b**, π^{NSO} is π bond energy of –N=S=O group, and π^{NSS} is π bond energy of –N=S=S group to be lost on cyclization. Substitution of reported values -86 and -65 kcal mol^{-1}[7)] for σ^{CO} and σ^{CS}, respectively, in the above equation gives $\pi^{\mathrm{NSS}} - \pi^{\mathrm{NSO}} = 25$ kcal mol^{-1}. Thus π-bond of –N=S=S group is weaker than that of –N=S=O group by, at least, 25 kcal mol^{-1}.

TABLE 2. SOLVENT EFFECT ON K AT 43 °C

Solvent	ε	$K=\dfrac{[\mathbf{1a}]}{[\mathbf{1b}]}$
Hexane	1.89	6.3
Cyclohexane	2.02	8.6
Carbon tetrachloride	2.23	9.2
Ethyl acetate	6.02	14.5
Dichloromethane-d_2	9.08	12.2
Acetone-d_6	20.7	17.7
Acetonitrile	37.5	25

Solvent Effect. Equilibrium constants at 43 °C in various solvents are shown in Table 2, where it is demonstrated that polar solvents greatly enhance the preference of cyclic isomer **1a**, suggesting that the dipole moment of **1a** is larger than that of the *N*-thiosulfinylaniline **1b**. Actually, the dipole moment of **1a** (*ca.* 2.9 D)[8a)] is larger than that of **1b** which was reasonably assumed to be nearly equal to the dipole moment of **6** (1.51 D).[8b)] Interestingly, quite a similar solvent effect has been reported for azido-tetrazole equilibria;[9)] in less polar solvents, the equilibrium is shifted towards the side of an azido form, suggesting that the dipole moment of an azido form is smaller than that of a tetrazole form. This situation is in line with the fact that dipole moment of phenyl azide (1.56 D)[10)] is smaller than that of 1,2,3-benzotriazole (4.10 D).[10)]

References

1) Y. Inagaki, R. Okazaki, and N. Inamoto, *Tetrahedron Lett.*, **1974**, 4575.

2) Y. Inagaki, R. Okazaki, and N. Inamoto, *Bull. Chem. Soc. Jpn.*, **52**, 1998 (1979).

3) For reviews, see R. N. Butler, *Chem. Ind. (London)*, **1971**, 371; M. Tisler, *Synthesis*, **1973**, 123; R. N. Butler, *Adv. Heterocyclic Chem.*, **21**, 323 (1977).

4) C. Temple, Jr., M. C. Thorpe, W. C. Coburn, Jr., and J. A. Montgomery, *J. Org. Chem.*, **31**, 935 (1966).

5) T. Sasaki, K. Kanematsu, and M. Murata, *Tetrahedron*, **27**, 5121 (1971).

6) D. H. R. Barton and M. J. Robson, *J. Chem. Soc., Perkin Trans. 1*, **1974**, 1245.

7) J. B. Hendrickson, D. J. Cram, and G. S. Hammond, "Organic Chemistry," 3rd ed, McGraw-Hill, New York (1970).

8) a) Y. Inagaki, R. Okazaki, and N. Inamoto, *Heterocycles*, **9**, 1613 (1978); b) Y. Inagaki, R. Okazaki, N. Inamoto, and T. Shimozawa, *Chem. Lett.*, 1978, 1217.

9) J. Elguero, R. Faure, J. P. Galy, and E. J. Vincent, *Bull. Soc. Chim. Belg.*, **84**, 1189 (1975); L. A. Burke, J. Elguero, G. Leroy, and M. Sana, *J. Am. Chem. Soc.*, **98**, 1985 (1976).

10) A. L. McClellan, "Tables of Experimental Dipole Moments," W. H. Feemen and Co., San Francisco (1963).