CHEMISTRY LETTERS, pp. 1781-1784, 1981.

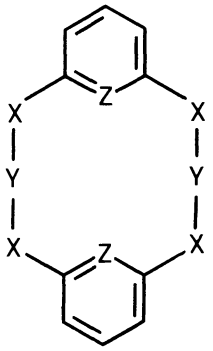
CONJUGATIVE FACTORS AFFECTING THE SYN-ANTI ISOMERIZATION RATE PROCESS OF 1,3,10,12-TETRATHIA[3.3](2,6)PYRIDINOPHANE

Francesco BOTTINO and Sebastiano PAPPALARDO*
Istituto Dipartimentale di Chimica e Chimica Industriale
dell'Università di Catania, Viale A. Doria 6, 95125 Catania ITALY

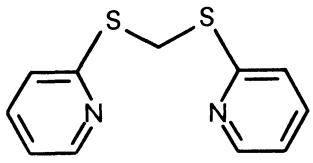
The synthesis and VT-NMR study of the title compound are described. A comparison of its conformational behaviour with that of related [3.3]metacyclophanes has led to the conclusion that, in addition to steric hindrance effects, conjugative factors may prove important in affecting the syn-anti isomerization of heteroheterophanes.

The stereochemical aspects of medium-sized cyclophanes have been of particular synthetic and theoretical interest for the past decades.[1] Extensive crystallographic[2] and NMR studies[3] have shown that [2.2]metacyclophanes[1c] and related heterocarbophanes[4] possess a stepped anti conformation. On the other hand, syn-anti isomerization has been reported in the larger [3.3]metacyclophanes,[5] the interconversion rate process being affected by several factors, such as the nature and position of the substituents,[5,6] non bonded interactions,[4a] geometry of the constituent aromatic moieties,[7] incorporation of heteroatoms on the bridges[8] and ring size.[5b]

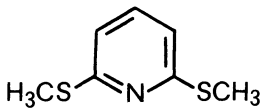
Recently, we have shown that the nature and geometry of the trisulphide bridges plays a major role in determining a different stereochemistry in hexathia[3.3]metacyclophanes 1 compared to related [3.3]metacyclophanes 2-4 having hydrocarbon bridges.[9]



	X	Y	Z
1	S	S	CH
2	CH_2	CH_2	CH
3	CH_2	S	CH
4	S	CH_2	CH
5	CH_2	S	N
6	S	CH_2	N



8



9

However, a further difference in our sulphur bridged metacyclophanes could arise from the property of the unshared electron pairs of the bridged sulphur atoms to develop a resonance interaction with the π-electrons of the aromatic rings,[10] eventually capable of raising the energy barrier to ring inversion.

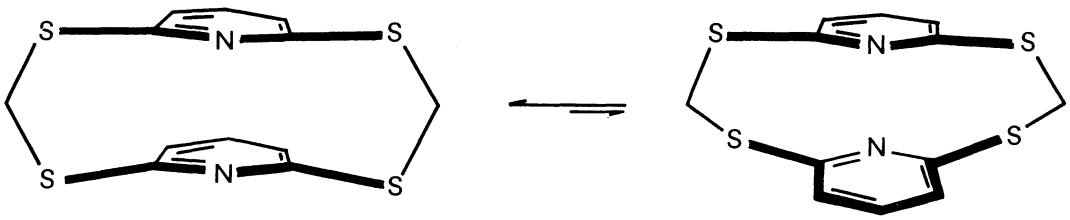
To prove the influence of conjugative factors on conformation and conformational changes, 1,3,10,12-tetrathia[3.3](2,6)pyridinophane 6 was synthetized and subjected to variable temperature NMR analysis.

Compound 6 was obtained by nucleophilic condensation of the dipotassium salt of 2,6-dimercaptopyridine with dibromomethane in refluxing ethanol, under highly dilute conditions. A pure sample of 6, yellow prisms, mp 195-197 °C, was isolated in very low[11] yield (5%) as the fastest moving component from the chromatography (benzene as an eluent) of the reaction mixture. Structure 6 was confirmed by its mass and NMR spectra.

The 80-MHz NMR spectrum ($CDCl_3$) of 6 at 50 °C displays double doublets at δ 7.21 and 6.87 for H-4 and H-3,5 pyridyl protons (J = 7.76), respectively, and a broad signal for the bridging methylene protons at δ 5.57.

In order to establish the conformational preference of 6, the chemical shifts of the pyridyl protons in 6 were compared to those of pertinent protons in model compounds di(2-pyridylthio)methane 8,[12] and 2,6-dithiomethoxypyridine 9. The NMR spectrum of 8 exhibited four distinct octects for pyridyl protons at δ 8.48 (H-6, J = 4.83, 1.90, 0.97 Hz), 7.49 (H-4, J = 7.92, 7.05, 1.90 Hz), 7.18 (H-3, J = 7.92, 1.26, 0.97 Hz) and 7.01 (H-5, J = 7.05, 4.83, 1.26 Hz), and a sharp singlet for methylene protons at δ 5.07, while that of compound 9 showed double doublets at δ 7.40 and 6.94 for H-4 and H-3,5 pyridyl protons (J = 7.90), respectively, and a singlet at δ 2.54 for thiomethoxy protons. The upfield shifts experienced by the pyridyl protons in 6 suggest that the syn conformation 6a is preferred.

The variable temperature NMR spectrum of 6 exhibits a sharpening of the methylene signal at elevated temperatures, while at -7 °C coalescence of this singlet occurred and at -50 °C two doublets at δ 7.11 and 4.25 (J = 14.4 Hz) were resolved. Based on these data, the syn-anti isomer interconversion 6a $\rightleftharpoons$ 6b was calculated to be $\Delta G_c^{\neq}$ = 12.2 kcal/mol.



6a 6b

Although this value is in agreement with related flipping of syn and anti conformers,[14] it is unexpectedly high if compared with those reported for related[3.3] metacyclophanes.[15] In fact, in the benzenophane series (compounds 2-4) the energy barrier for syn-anti isomerization decreases on increasing the ring size;[15] moreover, in the pyridinophane series (compounds 5-6) the steric hindrance in the transition state would be evidently least,[18] considering that the space occupied by the lone pair of electrons on the nitrogen atom of pyridine is smaller than that occupied by a hydrogen atom attached to a benzene nucleus.[1c] However, in spite of increased ring size and diminished steric hindrance, a higher free energy of activation was ascertained for 6.

This result provides evidence that a concerted conjugation of the unshared electron pairs of the bridged sulphur atoms with the π-electrons of the pyridine rings is operating in 6, which results in a percentage of double bond character of C_{Py}-S bonds, capable of restricting the rotational freedom of the heteroaromatic constituents, enhancing in the meantime its conformational preference.

References

1) (a) B. H. Smith, "Bridged Aromatic Compounds", Academic Press: New York, 1964; (b) D. J. Cram and J. M. Cram, Acc. Chem. Res., 4, 204 (1971); (c) F. Vögtle and P. Neumann, Angew. Chem., Int. Ed. 11, 73 (1972); (d) Synthesis, 1973, 85; (e) S. Misumi and T. Otsubo, Acc. Chem. Res., 11, 251 (1978); F. Vögtle and G. Hörner, Top. Curr. Chem., 74, 1 (1978).

2) C. J. Brown, J. Chem. Soc., 1953, 3278; A. W. Hanson, Acta Cryst., 15, 956 (1962); B. Kramenar and C. K. Prout, J. Chem. Soc., 1965, 4838; M. Mathew, Acta Cryst., 24B, 530 (1968).

3) See ref. 1c: ref. 9-17 therein.

4) (a) F. Vögtle and A. H. Effler, Chem. Ber., 102, 3071 (1969); (b) F. Vögtle, Tetrahedron Lett., 1968, 3623; (c) F. Bottino, S. Foti, S. Pappalardo, P. Finocchiaro, and M. Ferrugia, J. Chem. Soc. Perkin Trans. 1, 1979, 198; (d) F. Bottino and S. Pappalardo, Heterocycles, 12, 1331 (1979).

5) (a) F. Vögtle and L. Schunder, Chem. Ber., 102, 2677 (1969); T. Sato, M. Wakabayashi, K. Hata, and M. Kainosho, Tetrahedron, 27, 2737 (1971).

6) (a) R. H. Mitchell and V. Bookelheide, Tetrahedron Lett., 1970, 1197; (b) F. Vögtle, W. Wieder, and H. Förster, Tetrahedron Lett., 1974, 4361; (c) D. Kamp and V. Bookelheide, J. Org. Chem., 43, 3470 (1978).

7) F. Vögtle and R. Lichtenthaler, Chem. Ztg., 94, 727 (1970).

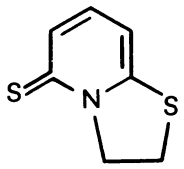
8) R. H. Mitchell, Tetrahedron Lett., 1975, 1363.

9) F. Bottino, S. Foti, S. Pappalardo, and N. Bresciani-Pahor, Tetrahedron Lett.,

1979, 1171; F. Bottino and S. Pappalardo, Tetrahedron, 36, 3095 (1980).

10) F. Bottino and S. Pappalardo, Org. Magn. Reson., 16, 1 (1981).

11) The enhancement in polar solvents, such as ethanol, of the tautomeric thione form of 2,6-dimercaptopyridine could account for the low yield of 6, as suggested by the formation of the thione 7 (15% yield) in the attempt to synthesize the higher homolog 1,4,11,14-tetra thia[4.4](2,6)pyridinophane by usual procedures.



7

7: yellow needles, mp 109-111.5 °C; MS (70 eV) m/e 169 (M^+, 100) NMR ($DMSO_{d6}$) δ 7.13 (m, pyr H, 2H), 6.80 (dd, pyr H, 1H, J = 6.4, 2.1 Hz), 4.77 (t, NCH_2, 2H, J = 7.5 Hz), and 3.55 (t, SCH_2, 2H, J = 7.2 Hz).

12) 90% yield, from the potassium salt of 2-mercaptopyridine and dibromomethane in refluxing DMF, colourless needles, mp 91-92.5 °C (from ethanol), lit.[13] mp 93-93.5 °C.

13) R. F. Brookes, J. E. Cranham, W. A. Cummings, D. Greenwood, B. S. Jackson, and H. A. Stevenson, J. Sci. Food Agr., 8, 31 (1957).

14) G. R. Newkome, A. Nayak, G. L. McClure, F. Danesh-Khoshboo, and J. Broussard-Simpson, J. Org. Chem., 42, 1500 (1977), and references therein.

15) For 2, $\Delta G_c^{\neq}$ = 11 kcal/mol;[16] for 3, less than 9.3 kcal/mol;[5b] no VT-NMR has been reported for 4.[17]

16) T. Shinmyozu, T. Inazu, and T. Yoshino, Chem. Lett., 1978, 1319; ref. 7 therein.

17) F. Vögtle and R. Lichtenthaler, Z. Naturforsch., 26b, 872 (1971).

18) Accordingly, the methylene protons in 5 appear as a singlet at δ 4.0 in the temperature range -50 ÷ +150 °C.[5a]

(Received September 3, 1981)