Solution Structure and Preferred Orientation of 3,7-Dibromo-10*H*-phenothiazine Dissolved in Nematic Liquid Crystal[†]

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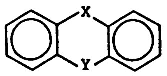
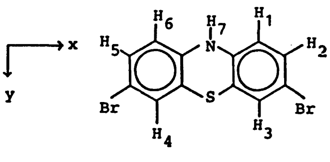
(Received August 14, 1987)

The NMR spectrum of the title compound has been measured in nematic phase ZLI1167 and analyzed to obtain the direct couplings. The direct couplings were interpreted by assuming a folded structure of the tricyclic framework. The dihedral angle of the two phenyl rings is determined to be 149.1±2.5° and a value of 170±3° is obtained for the angle of S···N-H. The NH proton is concluded to occupy a "equatorial" position on the central ring in a boat form. The preferred orientation of the molecule in ZLI1167 is discussed by comparing the principal axes of order tensor with those of the moment of inertia.

NMR studies of molecules oriented in liquid crystals provide important information on the molecular structure and preferred orientation in mobile state. These studies for some tricyclic compounds **1** folded along a symmetry axis have proved that the angle of folding (dihedral angle) changes depending on the state of compound investigated.[1—5] For example, dihedral angles of 131.4° in gaseous state,[6] 128° in crystals,[7,8] and 141.6°[2] and 140.6°[1] in solution (of nematic liquid crystals) have been reported for thianthrene (X=Y=S in **1**). These facts stimulate systematic works on structural parameters including the dihedral angle in the mobile state. In the present study, 3,7-dibromo-10*H*-phenothiazine (**2**) is taken up among derivatives of the phenothiazines. The tricyclic compounds phenothiazines are interested because they include a number of important drugs with tranquilizing, antihistaminic, and antiemetic activities.



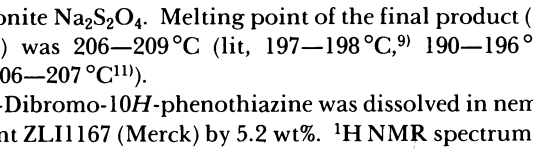
1
The tricyclic framework



2
3,7-Dibromo-10*H*-phenothiazine

Experimental

3,7-Dibromo-10*H*-phenothiazine was synthesized by the bromination of 10*H*-phenothiazine.[9] The raw product was recrystallized from toluene after decolorizing by sodium dithionite $Na_2S_2O_4$. Melting point of the final product (pale green) was 206—209 °C (lit, 197—198 °C,[9] 190—196 °C,[10] and 206—207 °C[11]).



3,7-Dibromo-10*H*-phenothiazine was dissolved in nematic solvent ZLI1167 (Merck) by 5.2 wt%. ^1H NMR spectrum was measured on a XL-200 NMR spectrometer operating at 200 MHz. The temperature of measurement was 34.1 °C. Fids of 5000 transients were accumulated using a 40° (4 μs) pulse at an interval of 0.4 s and Fourier transformed to obtain a spectral width of 8 kHz for the data point of 16k. A convolution difference was taken to remove very broad background signals originating from the solvent. The resulting line width was ca. 10 Hz in the center and ca. 20 Hz at the edges of the spectrum. The preliminary spectra were considerably broadened probably because of a contamination with some metallic or radical impurities, and hence a small amount of 1,10-phenanthroline was added to obtain the final sharp spectrum. Normal spectrum in an isotropic medium was taken on a Hitachi R-22 NMR spectrometer in CW mode at 90 MHz and at the probe temperature of 34.1 °C. The solvent used was a mixture (20/80 in volume) of dimethyl sulfoxide and carbon tetrachloride which was suited for a better separation in chemical shifts.

Analysis of NMR spectra obtained in the nematic phase was made by the programs LAO3D9 and LAO3D9D. These programs are modified versions of LAOCN3 and applicable up to 9 spins. These versions have been written in double precision and LAO3D9D includes a damping route as reported by the authors.[5] The resulting direct couplings were analyzed by the program SHAPE[12] to obtain structural and order parameters. Only the variance in LAOCN calculation was input for the error analysis. All the above calculations were done on NEAC S-1000 and SX-1 computers at the Computation Center in Osaka University.

Results

3,7-Dibromo-10*H*-phenothiazine has C_s symmetry and exhibits spectra with the seven spin system of AA′BB′CC′D. It includes four chemical shifts (δ_1, δ_2, δ_3, and δ_7) and twelve direct couplings (D_{12}, D_{13}, D_{14}, D_{15}, D_{16}, D_{17}, D_{23}, D_{24}, D_{25}, D_{27}, D_{34}, D_{37}) besides the twelve indirect couplings J_{ij} as independent variables. Among these parameters the indirect couplings were fixed at the values observed in an isotropic medium as usually done[13] when the indirect couplings show no discernible solvent dependency. The values used were J_{12}=8.20 and J_{23}=2.20 Hz observed in the mixed solvent above mentioned, other indirect couplings being negligibly small. The LAOCN iteration calculation has given rms error of 1.35 Hz for the ninety seven of the observed and the simulated transition frequencies.

[†] NMR Study of Molecules in Anisotropic Systems. VI.

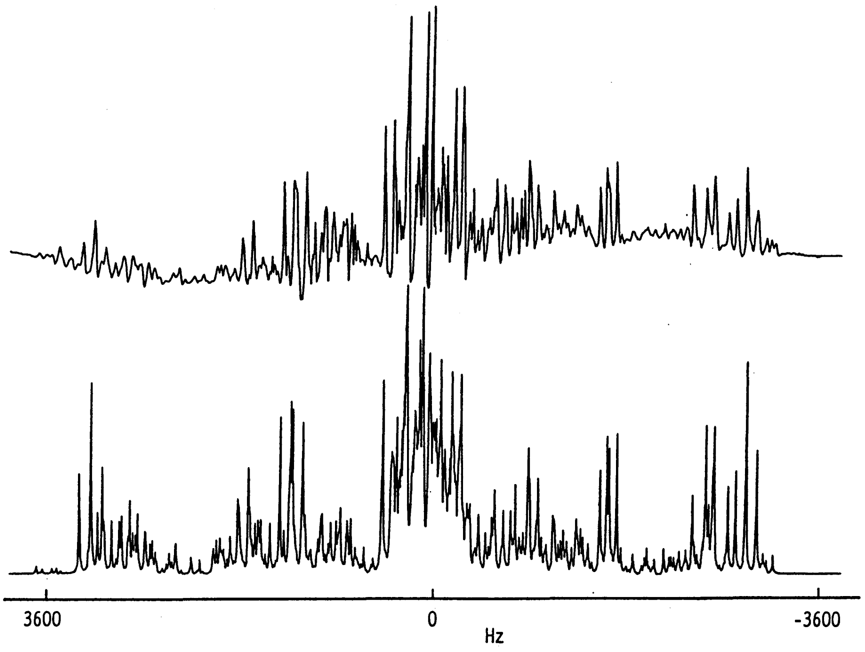


Fig. 1. Experimental(upper) and simulated(lower) NMR spectra of ^1H for 3,7-dibromo-10*H*-phenothiazine dissolved in nematic solvent ZLI1167.

Table 1. NMR Parameters of 3,7-Dibromo-10*H*-phenothiazine Dissolved in Nematic Phase ZLI1167

Direct coupling/Hz:			
D_{12}	822.91±0.14	D_{34}	97.82±0.17
D_{13}	58.97±0.22	D_{37}	56.17±0.21
D_{14}	32.65±0.24		
D_{15}	45.97±0.19	Chemical shift/Hz:[a)]	
D_{16}	161.49±0.40	ν_1	−67.32±0.25
D_{17}	1026.67±0.15	ν_2	48.01±0.24
D_{23}	98.65±0.20	ν_3	68.36±0.23
D_{24}	23.77±0.21	ν_7	331.08±0.35
D_{25}	21.77±0.29		
D_{27}	135.22±0.22		

a) Given in Hz at 200 MHz relative to the carrier frequency. Positive toward the low field side.

The simulated spectrum is shown in Fig. 1 together with that observed. The experimental line width is broader at the edges of the spectrum. This is caused by a temperature fluctuation on the sample and also probably by a trace amount of impurities which remain unmasked even on addition of 1,10-phenanthroline. The NMR parameters determined are listed in Table 1. The chemical shifts of H_2 and H_3 are reversed in order in the nematic phase compared to those in an isotropic medium where $\delta_2-\delta_1=0.356$ ppm, $\delta_3-\delta_1=0.267$ ppm, and $\delta_7-\delta_1=1.889$ ppm have been obtained in the above mixed solvent. This may be due to a solvent effect. The direct couplings obtained are analyzed by the program SHAPE. The resulting order parameters and the structural parameters are listed in Table 2 (case 1).

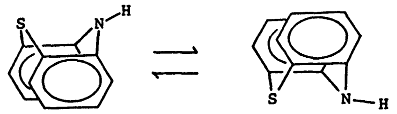
Table 2. Structural Parameters and Order Parameters of 3,7-Dibromo-10*H*-phenothiazine Dissolved in ZLI1167

	Case 1[a)]	Case 2[a)]	10*H*-phenothiazine[a)]
Distance ratio			
r_{13}/r_{12}	2.089±0.014	2.092±0.013	1.979
r_{14}/r_{12}	2.943±0.017	2.958±0.013	2.860
r_{15}/r_{12}	2.856±0.024	2.854±0.025	2.835
r_{16}/r_{12}	1.907±0.019	1.904±0.018	1.902
r_{17}/r_{12}	1.003±0.014	1.003±0.013	0.969
r_{23}/r_{12}	1.943±0.039	1.952±0.045	1.750
r_{24}/r_{12}	3.497±0.044	3.525±0.055	3.368
r_{25}/r_{12}	3.753±0.036	3.753±0.036	3.697
r_{27}/r_{12}	1.927±0.019	1.929±0.020	1.858
r_{34}/r_{12}	2.253±0.022	2.296±0.041	2.240
r_{37}/r_{12}	2.171±0.025	2.175±0.027	2.248
Angle			
ϕ_0[b)]	150.6±2.1	149.1±2.5	158.5
θ_0[c)]	172.7±3.1 (171.4±3.1)	170.5±3.4 (169.3±3.4)	181.9
Order parameter[d)]			
S_{xx}	−0.1219±0.0003	−0.1223±0.0009	
S_{zz}	0.1798±0.0023	0.1834±0.0013	
S_{yz}	0.0672±0.0177	0.0659±0.0234	

a) Case 1: The ring inversion motion is not included in the SHAPE calculation. Case 2: The ring inversion motion is included. 10*H*-phenothiazine: Crystal data are cited for the parent compound(orthorhombic)[19] because such data are lacking for the dibromo derivative. b) The dihedral angle. c) The angle of S···N-H. See text for detail. d) r_{12}=2.356 Å assumed.[19]

Discussion

The framework of phenothiazine is known to be folded and to interconvert very rapidly between two equivalent structures:



The barrier to inversion is reported to be 2.87[14] and 2.4[15] kcal mol^{-1} for 10*H*-phenothiazine from dielectric relaxation studies, but no data are available for the dibromo derivative. In the above calculation (case 1 in Table 2), the barrier to this inversion is assumed to be so high that only the ground state is occupied at the measurement temperature. In this regard, correlation between the internal motion and the overall molecular reorientation[16–18] can affect the calculation. When the barrier to internal motion is very low and the rate of internal motion is much faster than that of the whole molecular reorientation, only a set of the order parameters is sufficient to describe the orientational behavior of the molecule and the molecular structure reflects a statistical average of the fast internal motion. This is the case for the internal rotation of methyl group. But when the rate of internal motion is comparable to or slower than that of the whole molecular reorientation, order parameters can differ in each step of the internal motion and in principle an infinite number of the order parameters are needed. In the present study, calculations were also attempted under the fast inversion limit: a potential function of Eq. 1 was adopted,

$$V=V_0\{(\psi/\psi_0)^4-2(\psi/\psi_0)^2\},\quad \psi=(\pi-\phi)/2 \qquad (1)$$

where V_0 is the inversion barrier and ϕ is the dihedral angle between the two phenyl rings, ϕ_0 being this angle at ground state. An alternative function is proposed by Higashi et al.,[15] which has a singular point at $\phi=\pi$ and is not used here. Statistical averaging of the direct couplings under such inversion motion can be achieved by following equation

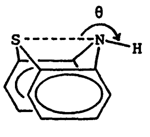
$$\langle D_{ij}\rangle=\int D_{ij}(\psi)P(\psi)\,\mathrm{d}\psi \qquad (2)$$

where $\langle\ \rangle$ means the statistical average and where D_{ij} (ψ) and $P(\psi)$ are the direct coupling and the distribution function, respectively, calculated under a dihedral angle of ϕ. This distribution function is given by Eq. 3.

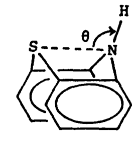
$$P(\psi)\,\mathrm{d}\psi=\exp(-V/RT)\,\mathrm{d}\psi/\int\exp(-V/RT)\,\mathrm{d}\psi \qquad (3)$$

To perform the integration in above equations, ϕ was changed from 80° to 180° in 0.1° step and integrated numerically. Subroutines were added to SHAPE for this calculation: DIHED to calculate the dihedral angle for the ground state, XYZIM to give new coordinates for the dihedral angles changed stepwise, and CALCUD to derive the direct couplings for the variable dihedral angles. Only one set of the order parameters are defined since the very rapid rate of the inversion motion is assumed. The barrier was set equal to 2.4 kcal mol^{-1}. An effort to determine this barrier from the simulation of the direct couplings was unsuccessful. The results of calculation are also summarized in Table 2 (case 2). The weighted rms error between the observed and the simulated direct couplings was almost the same in the two cases, i.e., 0.240 Hz (case 1) and 0.239 Hz (case 2). In fact, the recalculated values of D_{ij} were the same in the two cases, and only those of D_{15}, D_{24}, and D_{25} deviated from the experimental values by slightly more than their probable errors, i.e., D_{15}=46.45, D_{24}=23.30, and D_{25}=21.19 Hz. Therefore, it may be concluded that the experimental values of D_{ij} have failed to distinguish between the two cases because of their relatively large errors coming from the line broadening in the spectrum. A more elaborate analysis of the direct couplings assuming a correlation between the inversion and the whole molecular reorientation was not attempted, since the barrier to inversion was not known for the dibromo derivative and the experimental values of D_{ij} were not so accurately obtained as to make the barrier determinable in that analysis. However, the structural parameters and the order parameters derived above deserve further discussion as described below.

Molecular Structure of 3,7-Dibromo-10*H*-phenothiazine Dissolved in ZLI1167. The dihedral angle (ϕ_0) and the angle of S$\cdots$N-H (θ) in the ground state are listed in Table 2. The latter angle is determined assuming that N and S atoms lie just on the coplanar line made by the two planes of phenyl ring and assuming that r_{NH}=1.09 Å.[19] This angle is also determined for the case when N and S stoms deviate from the coplanar line by 0.03 and 0.18 Å, respectively, and r_{SN} equals 3.03 Å as reported in crystal.[19] This value is listed in parenthesis in Table 2. Also listed in the Table are structural parameters in an orthorhombic crystal of 10*H*-phenothiazine for reference. The dihedral angle in a little smaller in the dibromo derivative than that in the parent molecule in Table 2. This angle in the latter compound is also reported to be 153.3°[20] in monoclinic crystal and 144±7°[21] in solution. Hitherto, much effort has been devoted to study the conformation of phenothiazines. However, some controversies still remain unresolved especially regarding the conformation of the NH proton. For 10*H*-phenothiazine a molecular orbital calculation predicted superiority of the "H-intra" conformer in the stability compared to the "H-extra" one,[22] and this was proved in crystal.[19,20] However, the conformation in the crystal does not necessarily indicate the stability of a molecule in itself since the molecule is embedded



"H-intra" form



"H-extra" form

in a rigid lattice in the crystal. In solution a molecular Kerr constant study supported the "H-intra" conformation[21] and NMR chemical shifts did not conflict with this conclusion.[23] However, coexistence of "H-intra" and "H-extra" conformers was suggested from a dipole moment study.[24] In the present case of 3,7-dibromo-10*H*-phenothiazine, the angle of S ··· N-H is less than 180° and might indicate the "H-extra" conformation.[25] However, in a pure "H-extra" conformation, the angle of S ··· N-H needs to be in close vicinity to 90° since the proton is situated at an "axial" position of the central ring in the boat form. In this sense, discussion of the stability of the two conformers made on the basis of the S ··· N-H angle is confusing.[26] This angle lies between 150° and 185° in various phenothiazines[25] including the present case. These values deviate far from 90° and it may be said that the phenothiazine derivatives are supported to be in the "equatorial" conformation irrespective of the substituent attached to nitrogen, although the position of the substituent is changed from one derivative to another. With regard to the dihedral angle and the conformation of NH proton, a similar NMR study using liquid crystal solvent is interested for 10*H*-phenothiazine itself. However, some special techniques such as multiple quantum NMR spectroscopy or high power decoupling for some deuterated compounds are needed to simplify the spectrum.

Preferred Orientation of 3,7-Dibromo-10*H*-phenothiazine Dissolved in ZLI1167. The authors have demonstrated on an interrelation between the principal axes for the order tensor and those for the moment of inertia in the studies of hexachlorocyclohexane isomers.[27,28] In the present case, principal axes x',y',z' for the order tensor can be derived as follows. The axis x' coincides with x from symmetry. The axes y' and z' are those which makes $S_{y'z'}$ equal to zero. $S_{y'z'}$ is expressed as in Eq. 4,

$$S_{y'z'}=\sum_{p,q} \cos\theta_q^{z'}S_{pq}, \quad p,q=x,y,z \tag{4}$$

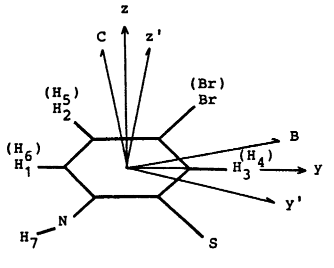


Fig. 2. Principal axis systems for the order tensor (x',y',z') and for the moment of inertia(A,B,C) in 3,7-dibromo-10*H*-phenothiazine (side view).
The x' and A axes coincide with the x axis from the C_s symmetry, but these three axes are abbreviated in the Figure for simplicity. The x, y, and z axes are defined so as to place the protons of H_1, H_3, H_4, and H_6 on the xy plane. Angles of rotation are −11.7° for y' and z' axes and 11.3° for B and C axes with regard to the y and z axes.

where $\theta_p^{y'}$ means the angle between axes p and y'. From this equation, an angle of rotaion ω which moves y and z on to y' and z', respectively, can be obtained as,

$$\tan(2\omega)=2S_{yz}/(S_{yy}-S_{zz}) \tag{5}$$

and also the relevant principal values turn out to be: $S_{x'x'}=S_{xx}$ and $S_{z'z'}=\sin^2\omega S_{yy}+\cos^2\omega S_{zz}-\sin(2\omega)S_{yz}$. From these equations, $\omega=-11.7$, $S_{x'x'}=-0.1223$, and $S_{z'z'}=0.1995$ are reached (Fig. 2). Principal axes A, B, C for the moment of inertia were determined by the program XYZ[29] modified by the present author, principal values being $I_A=513.0$, $I_B=5671.3$, and $I_C=6003.7$ amu · Å^2. In this calculation, bond lengths obtained in a crystal,[19] bonding angles of 120° for carbons, an angle of 170.5° for S ··· N-H, and the dihedral angle of 149.1° were used together with the angles of 66.0° for <S-N-C and 54.0° for <N-S-C. The B and C axes are seen to be rotated by 11.3° from y and z axes (Fig. 2). Therefore, the two principal axis systems differ 23° from each other, suggesting a special steric effect of Br atoms on the phenyl rings as observed[27,28] for Cl stoms in hexachlorocyclohexane.

The author (H. F.) is grateful to Professor Kensuke Takahashi of Nagoya Institute of Technology for facilities for the NMR measurements

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26) Bonding angles around the N atom change considerably reflecting the degree of conjugation of N with the phenyl rings. And so, the two conformers are better differentiated from whether the H atom is located closer to the phenyl rings ("H-intra") or the lone pair electrons are ("H-extra"). This condition is well judged on a basis of the angle between the N-H bond and the plane made by the N atom and the two phenyl carbons attached to it.

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