

## The Dihedral Angle of 2-(Trifluoromethyl)phenothiazine (1)

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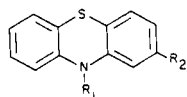
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The structure of 2-(trifluoromethyl)phenothiazine,  $C_{13}H_8NSF_3$ , was determined by single crystal X-ray diffraction. The molecule crystallizes in space group  $P2_12_12_1$ , with  $a = 7.766(2)$ ,  $b = 5.957(1)$ , and  $c = 23.499(5)\text{\AA}$ . The final R value is 0.073. The CSC bond angle is  $102.0^\circ$ , the CNC bond angle is  $124.8^\circ$ , and the dihedral angle between the phenylene planes is  $171.2(1)^\circ$ . The hydrogen atom bonded to the nitrogen atom was located; it is on the inside of the butterfly angle and the S...N-H bond angle is  $173.3^\circ$ .

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The structures of substituted phenothiazine molecules are of interest because of the relationships between



molecular structures and pharmacological activity for the phenothiazine "tranquilizer" drug compounds. Previous structural work (2, and references therein) has shown the dihedral angle between the phenylene groups (the "butterfly" angle) is the structural parameter which varies most significantly from one derivative to another. The crystal structure of the important drug triflupromazine (2) ( $R_1 = (CH_2)_3N(CH_3)_2HCl$ ,  $R_2 = CF_3$ ) has two crystallographically independent molecules, with butterfly

angles of  $134.4 \pm .05^\circ$  and  $141.0 \pm .05^\circ$ ; the difference in these angles appears to be influenced by the solid state packing. In order to make another determination of the structural features of a phenothiazine unit with the highly electronegative  $CF_3$  substituent, the crystal structure of 2-(trifluoromethyl)phenothiazine ( $R_1 = H$ ,  $R_2 = CF_3$ ) (hereafter TFP) was undertaken. This structural study was also initiated because of interest in the position of the

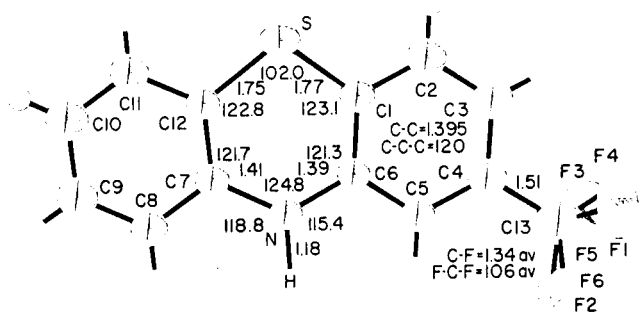


Figure I. Molecular Structure of 2-(trifluoromethyl)phenothiazine.

In this view the phenylene groups are bent down from the S...N line, (away from the eye of the viewer) and the H(N) atom is farther away from the viewer's eye than the nitrogen atom.

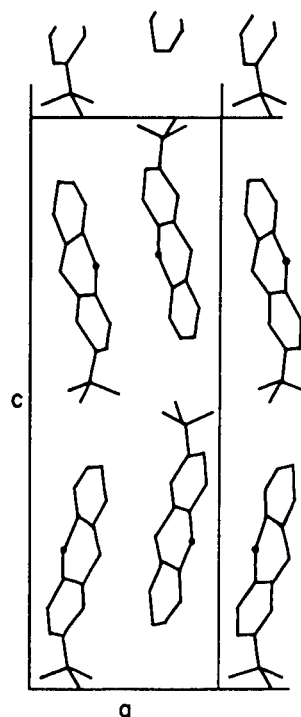


Figure II. Crystal Packing of 2-(trifluoromethyl)phenothiazine.

Table I

## Crystal and Refinement Data

|                    |                  |   |       |
|--------------------|------------------|---|-------|
| Formula            | $C_{13}H_8SNF_3$ | F. W.   | 267.3 |
| Space Group        |                  | P2 <sub>1</sub> 2 <sub>1</sub> 2 <sub>1</sub> .   |       |
| Cell Constants     |                  | a = 7.766(2), b = 5.957(1), c = 23.499(5) Å, V = 1133 Å <sup>3</sup> (from 12 carefully centered diffractometer reflections, at 22°C) |       |
| Measured Density   |                  | 1.59(2) g cm <sup>-3</sup> (suspension in C <sub>4</sub> H <sub>9</sub> Br - CCl <sub>4</sub> mix)                                    |       |
| Calculated Density |                  | 1.57 g cm <sup>-3</sup> for Z = 4 (imposes no symmetry on the molecule)   |       |
| Crystal Dimensions |                  | 0.08 x 0.18 x 0.45 mm (all ± 0.01 mm) in the (001), (100), and (110) directions. Mounted on b.  |       |

*Diffractometer Data*

$\mu(\lambda = 0.71069 \text{ \AA}) = 3.1 \text{ cm}^{-1}$ .

Transmission coefficients = 0.97-0.99 (no correction)

Manually operated GE XRD-5 diffractometer. MoK $\alpha$  x-rays filtered with 1-mil Zr.

$\theta$ - $2\theta$  scan of 2° in  $2\theta$  at 2°/min, 20 sec. stationary backgrounds

640 unique data measured ( $2\theta < 50^\circ$ ); 286 with  $I > 2 \sigma(I)$

Four reflections measured periodically during 2 day data collection indicated electronic and crystal stability.

$\sigma(I) = (S + 2.25B + 0.0016 I^2)^{1/2}$  where S = scan count, B = B<sub>1</sub> + B<sub>2</sub> (sum of background counts) and I = S - 1.5B.

If  $|B_1 - B_2| > 2\sigma(I)$  (above),  $\sigma(I) = 1.5 |B_1 - B_2|$

*Film Data*

$\mu(\lambda = 1.5418 \text{ \AA}) = 27.4 \text{ cm}^{-3}$

Transmission coefficients = 0.75-0.90 (correction made) (6)

Weissenberg multiple-film techniques, h0 $\bar{k}$ -h4 $\bar{k}$  CuK $\alpha$  x-rays filtered with 1-mil Ni. Layer data merged using overlapping diffractometer data.

*Refinement Data*

Neutral atom scattering factors for C,H,N,S,F (7) Anomalous dispersion corrections for S (8).

Two reflections (200 and 112) given zero weight because of extinction evidence.

Calculations done with IBM 370/150 computer at University of Arkansas Computing Center, using programs previously described (9).

hydrogen atom bonded to the nitrogen; thus far only two of the phenothiazine structures reported have been unsubstituted at the nitrogen: phenothiazine (3) and 2-methoxyphenothiazine (4). Both of these molecules have a large dihedral angle, which has been related to special features of the hydrogen position (5), but in only one study was the hydrogen atom located (4).

The bond distances and bond angles of interest in TFP are given in Figure I; the estimated standard deviations are 0.01 Å for bond distances and 0.8° for bond angles (see below for a discussion of the molecular constraints used during refinement). The dihedral angle between the phenylene planes is  $171.2 \pm 0.1^\circ$  and the sulfur and nitrogen atoms are displaced from the plane of the phenylene group containing Cl by  $0.17 \pm 0.1^\circ$  and  $0.11 \pm 0.2^\circ$ , respectively, and from the plane of the phenylene group containing C7 by  $0.09 \pm 0.1^\circ$  and  $0.06 \pm 0.2^\circ$ , respectively. Displacements of these magnitudes are commonly found in phenothiazine structures (2); the sulfur and nitrogen atoms are displaced toward the

outside of the dihedral angle, as is also typical. If the S and N atom positions are included with each of the phenylene groups for a calculation of weighted best-fit planes, the dihedral angle is  $168.3 \pm 0.1^\circ$ . Thus the butterfly angle of TFP reported here is much more nearly planar than any previously reported uncomplexed phenothiazine derivative. The major factor causing this near-planarity of the ring system is probably the electron withdrawing effect of the highly electronegative CF<sub>3</sub> group; the crystal packing is void of any significant intermolecular contact which would contribute to the flattening of the molecule. All intermolecular distances of non-hydrogen atoms are greater than the sum of the van der Waals radii for the atoms involved, and no intermolecular contact involving hydrogen is more than 0.1 Å shorter than the van der Waals contact distance (using a value of 1.2 Å for hydrogen). A drawing of the crystal packing is given in Figure II

The nitrogen-bonded hydrogen atom, located by use of difference maps, is on the inside of the butterfly

Table II

Final Positional and Thermal Parameters for Trifluoromethylphenothiazine

| Atom    | x          |            | z           | B(A <sup>2</sup> ) |
|---------|------------|------------|-------------|--------------------|
| S       | 0.1666 (5) | 0.1103 (6) | 0.2439 (1)  | ---                |
| F (1)   | 0.252 (2)  | -0.308 (2) | -0.0056 (6) | ---                |
| F (2)   | 0.314 (2)  | -0.606 (2) | 0.0370 (5)  | ---                |
| F (3)   | 0.048 (2)  | -0.525 (2) | 0.0227 (6)  | ---                |
| N       | 0.345 (1)  | -0.351 (2) | 0.2295 (3)  | 2.9 (2)            |
| F (4)   | 0.151      | -0.314     | -0.006      | 7.0                |
| F (5)   | 0.111      | -0.627     | 0.036       | 7.0                |
| F (6)   | 0.366      | -0.494     | 0.028       | 7.0                |
| C (1)   | 0.169      | -0.066     | 0.186       | 3.2 (3)            |
| C (2)   | 0.092      | 0.020      | 0.139       | 4.1 (3)            |
| C (3)   | 0.104      | -0.100     | 0.090       | 4.3 (3)            |
| C (4)   | 0.191      | -0.305     | 0.089       | 3.9 (3)            |
| C (5)   | 0.267      | -0.391     | 0.136       | 3.2 (3)            |
| C (6)   | 0.256      | -0.271     | 0.184       | 2.8 (3)            |
| C (7)   | 0.320      | -0.275     | 0.284       | 3.0 (3)            |
| C (8)   | 0.385      | -0.407     | 0.326       | 3.6 (3)            |
| C (9)   | 0.369      | -0.333     | 0.379       | 4.4 (4)            |
| C (10)  | 0.290      | -0.128     | 0.391       | 4.9 (4)            |
| C (11)  | 0.225      | 0.003      | 0.349       | 3.9 (3)            |
| C (12)  | 0.241      | -0.071     | 0.295       | 2.9 (3)            |
| C (13)  | 0.203      | -0.434     | 0.036       | 5.8 (5)            |
| H (C1)  | 0.327      | -0.530     | 0.135       | ---                |
| H (C2)  | 0.033      | 0.160      | 0.140       | ---                |
| H (C3)  | 0.052      | -0.042     | 0.058       | ---                |
| H (C8)  | 0.439      | -0.547     | 0.318       | ---                |
| H (C9)  | 0.413      | -0.422     | 0.408       | ---                |
| H (C10) | 0.279      | -0.079     | 0.427       | ---                |
| H (C11) | 0.171      | 0.143      | 0.356       | ---                |
| H (N)   | 0.427      | -0.515     | 0.222       | ---                |

Anisotropic-thermal parameters ( $\times 10^3$ ) (a)

| Atom  | $\beta_{11}$ | $\beta_{22}$ | $\beta_{33}$ | $\beta_{12}$ | $\beta_{13}$ | $\beta_{23}$ |
|-------|--------------|--------------|--------------|--------------|--------------|--------------|
| S     | 22 (1)       | 20 (1)       | 1.9 (1)      | 5 (1)        | 0.0 (2)      | -0.4 (3)     |
| F (1) | 42 (5)       | 43 (6)       | 2.0 (3)      | -21 (5)      | -2 (1)       | 1 (1)        |
| F (2) | 28 (4)       | 44 (6)       | 2.3 (3)      | 1 (5)        | 0 (1)        | -5 (1)       |
| F (3) | 15 (3)       | 49 (7)       | 2.9 (4)      | -6 (4)       | 0 (1)        | -4 (1)       |

(a) Anisotropic thermal parameters defined by  $\exp -(\beta_{11}h^2 + \beta_{22}k^2 + \beta_{33}l^2 + 2\beta_{12}hk + 2\beta_{13}hl + 2\beta_{23}kl)$ .

angle and forms an S...N-H bond angle of  $173.3^\circ$ . This angle and position are the same as those found in the methoxyphenothiazine structure (4).

The nearly planar dihedral angle of TFP and the more exactly equatorial position of the H(N) atom provide strong support for the bonding rationale of the phenothiazines, which ascribes the equatorial hydrogen position to be a result of participation of the nitrogen atom's lone pair of electrons in the pi bonding system of the central ring (5).

## EXPERIMENTAL

Suitable crystals of TFP were obtained by slow evaporation of

a methylene chloride-hexane-octane (5:3:1) mixed solvent solution. Crystal data are given on Table I. Because of the paucity of diffractometer data (only 286 "observed" reflections) long exposure film methods were used to obtain 201 additional reflections.

The structure was solved by Patterson and Fourier techniques. The trifluoromethyl group is disordered; the two triplets of fluorine atoms are related by a rotation about the 3-fold axis of  $38^\circ$ , and have occupancy factors of 0.645 and 0.355. High correlations between adjacent fluorine atoms in the least squares refinement necessitated the refinement of the fluorine atom set with the low occupancy factor as a freely rotating group constrained to a triangular configuration. The phenylene rings were also refined as rigid groups, with variable individual atom temperature factors. The nitrogen-bonded hydrogen atom was clearly shown on a different map; neither its position or temperature factor were refined in the least squares. Use of anisotropic thermal parameters for the sulfur atom and the three 0.645 fluorine atoms is significantly well above the 99.5% level according to the R ratio test of Hamilton (10). All other atoms were refined with isotropic thermal parameters (thermal parameters of the hydrogen atoms and the 0.355 fluorine atoms were not allowed to vary).

In the final cycle of full-matrix least-squares refinement, no positional or thermal parameter shifted more than  $0.6\sigma$ . The final  $\Delta/\sigma$  show no apparent dependence on  $\theta$  or F or origin of data, thus the weighting scheme seemed reasonable. The film-diffractometer data merge appears satisfactory since the standard deviation of unit weight for the 286 diffractometer reflections is 0.9 and for the 201 film data reflections is 0.8. Only twelve reflections in the final refinement had  $\Delta F/\sigma$  greater than 2.0. A final difference Fourier of the asymmetric unit showed no peak height greater than  $0.34e^-/\text{\AA}^3$ , which is equal to 6% of the peak value of a carbon atom on the final Fourier map. The final values of  $R = 0.073$  and  $R_{\text{wtd}} = 0.064$  were not lowered significantly when the rigid group constraints were removed.

The final positional and thermal parameters are given in Table II.

## REFERENCES AND NOTES

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