The Crystal and Molecular Structure of Phenothiazine-10-propionitrile. The Effect of Crystal Packing on the Dihedral Angle of Phenothiazine Heterocycles

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Phenothiazine-10-propionitrile, $C_{12}H_8SNC_2H_4CN$, crystallizes in the centrosymmetric monoclinic space group $P2_1/n$, with a = 5.785(1)Å, b = 15.427(3)Å, c = 14.497(4)Å, β = 92.50(1)°, Z = 4, D_{meas} = 1.29(1) g cm^3 and D_{calc} = 1.28 g cm^3 at 23°. Three dimensional X-ray data were collected with a manual diffractometer using MoKα (λ 0.71069Å) radiation and by multiple film Weissenberg techniques using CuKα (λ 1.5418Å) radiation. The structure was determined by Patterson and Fourier methods and refined with 519 observed reflections by full matrix least-squares methods to an R of 0.077. The dihedral angle between the two planes of the *o*-phenylene rings is 135.4(3)°. In the folded heterocyclic ring the C-S-C angle is 97.8(7)° and the average C-S bond is 1.76(1)Å. A comparison of this structure to that of phenothiazine-10-propionic acid shows the two chemically similar molecules have the same dihedral angles in spite of completely different solid state packing patterns.

Introduction.

Phenothiazine drugs play a vital part in chemotherapy, and a good understanding of their structural properties will be necessary in order to elucidate their interactions with living organisms. A number of X-ray diffraction studies have been carried out on phenothiazine derivatives and related heterocyclic systems (1,2). These studies show the angle of fold of these bi-planar molecules is a sensitive function of the heteroatoms of the central ring and the ring substituents. This molecular parameter thus becomes a key structural feature which not only describes the gross molecular structure, but is also a measure of subtle electronic effects within the molecule. One of the concerns, however, with a strong emphasis on this type of structural feature is the question of its dependence on the solid state packing forces. We have recently (1) reported the crystal structure of phenothiazine-10-propionic acid, a simple *N*-substituted phenothiazine. As a check of the structural variations which occur in the crystal packing of these molecules, we report here the structures of phenothiazine-10-propionitrile for comparison with the

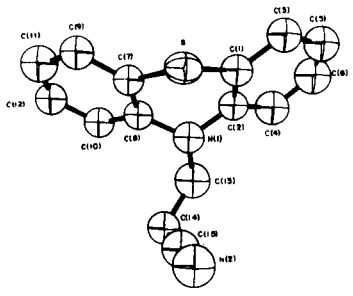


Figure 1a. The phenothiazine-10-propionitrile molecule numbering scheme.

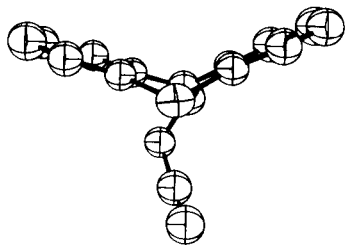


Figure 1b. Side view of the phenothiazine-10-propionitrile molecule, showing the dihedral angle.

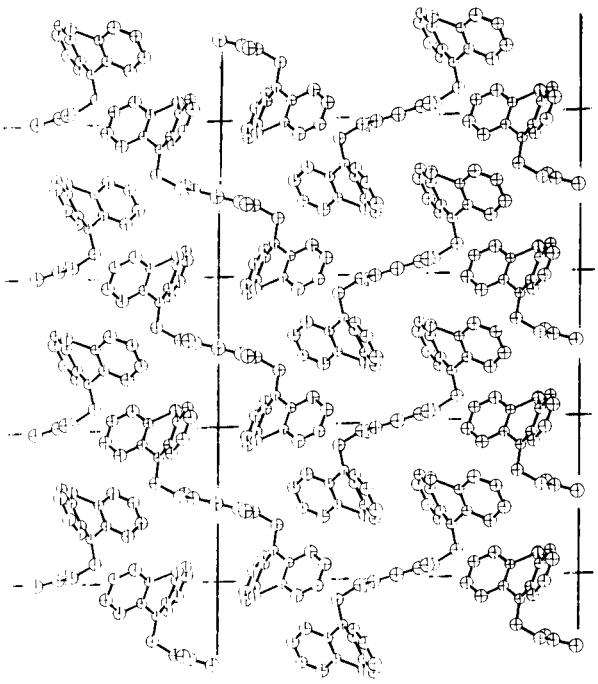


Figure 2a. Projection of the acid unit cell on the yz plane.

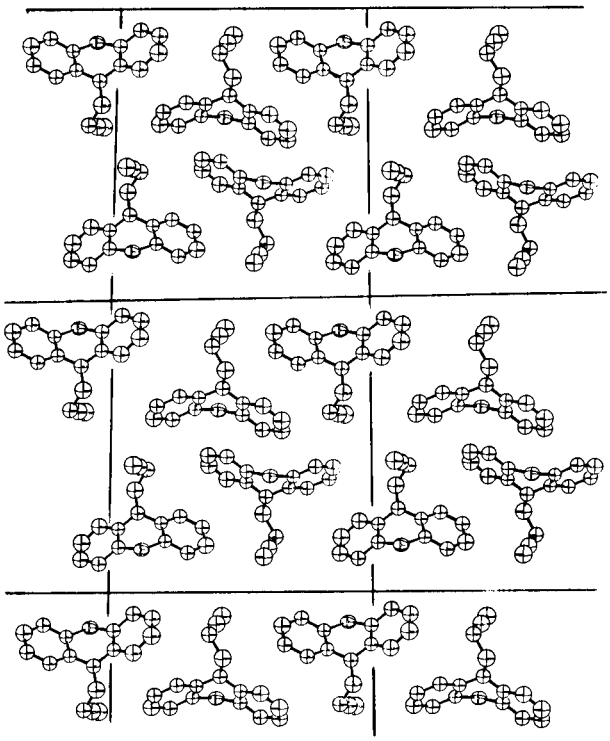


Figure 2b. Projection of the nitrile unit cell on the yz plane.

In both of these projections the +y direction is up and +z direction is to the right. The lines are the cell edges.

propionic acid structure. The general steric and electronic features of these two phenothiazine moieties are similar, but the crystal packing of the two molecules is very different because of the strong intermolecular hydrogen-bonding which dominates the packing of the acid molecule and is not possible for the nitrile.

Data Collection and Reduction.

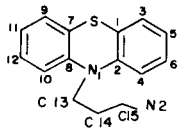
The colorless crystals of $C_{12}H_8SNC_2H_4CN$ (3) melt at 153°, and the molecular formula was confirmed by a mass spectrum of the crystals. Preliminary Weissenberg photographs taken with CuKα (λ = 1.5418Å) radiation indicated that the crystals belong to the monoclinic system with systematic absences [(h01) — h + 1 odd; (0k0) reflections — k odd] consistent with the space group $P2_1/n$ (no. 14).

Intensity data were collected from a needlelike crystal of dimensions 0.52 x 0.22 x 0.06 mm (all ± 0.01 mm) in the [100], [001], and [010] directions, respectively. The crystal was mounted with the *a* axis approximately parallel to the φ axis. Lattice constants were calculated by least-squares refinement (4) of the setting angles of 19 carefully centered reflections (MoKα radiation, λ = 0.71069Å). The cell parameters a = 5.785(1)Å, b = 15.427(4)Å, c = 14.498(4)Å, and β = 92.50(1)° give a unit cell volume of 1292.9Å^3 and a calculated density of 1.283 g/cm^{-3} for $C_{12}H_8SNC_2H_4CN$ with Z = 4. The observed density measured by flotation in a mixture of chlorobenzene and *n*-butyl bromide at 23° is 1.29(1) g/cm^{-3}.

Reflection data were obtained using both a G.E. quarter-circle manually-operated XRD-5 diffractometer and Weissenberg film techniques. For the diffractometer data the MoKα (λ = 0.71069Å) radiation was filtered with 1 mil zirconium foil. Each reflection was scanned 1.5° in 2θ at a scan rate of 2° per minute. The take-off angle was 3°. Stationary crystal-stationary counter background readings were taken for 20 seconds at each end of the scans. All peaks $0 < 2\theta < 40°$ were scanned. Of the 1340 reflections in this MoKα sphere only 303 had intensities greater than 1.5σ. These were considered the observed diffractometer data. The equation used for the standard deviation of the diffractometer data is $\sigma(I) = (S + BT^2 + 0.0016I^2)^{1/2}$ where S = total scan count, B = sum of the background counts, T = scan time/total background time and I = S-BT). For reflections in which

TABLE I

Final Atomic Position and Isotropic Thermal Parameters for $C_{12}H_8SNC_2H_4CN$



	X	Y	Z	B(Å²)
S	0.169(1)	0.131(1)	0.099(1)	----
N(1)	0.592(2)	0.236(1)	0.081(1)	5.4(3)
N(2)	0.243(2)	0.435(1)	0.071(1)	8.3(4)
C(1)	0.380(2)	0.147(1)	0.189(1)	4.7(3)
C(2)	0.573(2)	0.200(1)	0.172(1)	4.6(3)
C(3)	0.354(2)	0.108(1)	0.276(1)	5.4(3)
C(4)	0.746(2)	0.213(1)	0.244(1)	5.0(3)
C(5)	0.524(3)	0.122(1)	0.345(1)	7.3(4)
C(6)	0.708(2)	0.176(1)	0.332(1)	5.5(3)
C(7)	0.353(2)	0.126(1)	0.007(1)	5.0(3)
C(8)	0.553(2)	0.180(1)	0.005(1)	4.5(3)
C(9)	0.303(2)	0.069(1)	-0.069(1)	5.5(4)
C(10)	0.700(3)	0.178(1)	-0.071(1)	6.9(4)
C(11)	0.458(3)	0.074(1)	-0.143(1)	6.4(4)
C(12)	0.640(3)	0.123(1)	-0.141(1)	7.9(4)
C(13)	0.748(2)	0.310(1)	0.069(1)	7.4(4)
C(14)	0.670(2)	0.391(1)	0.120(1)	6.3(3)
C(15)	0.431(3)	0.416(1)	0.091(1)	7.1(4)
H(1)	0.202	0.066	0.287	5.0
H(2)	0.896	0.255	0.232	5.0
H(3)	0.505	0.091	0.413	5.0
H(4)	0.835	0.187	0.386	5.0
H(5)	0.147	0.025	-0.068	5.0
H(6)	0.860	0.222	-0.073	5.0
H(7)	0.415	0.032	-0.202	5.0
H(8)	0.748	0.120	-0.199	5.0
H(9)	0.630	0.370	0.200	5.0
H(10)	0.800	0.445	0.100	5.0
H(11)	0.910	0.330	0.075	5.0
H(12)	0.700	0.330	-0.010	5.0

In all tables, numbers in parentheses are the standard deviations for the last digit given. The hydrogen atom positions were calculated from the carbon atom positions and were not refined.

the two background readings differed by more than twice the calculated sigma due to tailing of the reflection peak, the standard deviations were set equal to the deviation of the background reading from the mean background value. Four standard reflections, measured at regularly spaced intervals, remained constant during the six day data collection and thus indicated crystal and electronic stability.

In order to rescue more of the weak reflection data, long exposure film data (0kl-5kl) were collected using multiple film, equi-inclination Weissenberg techniques with Ni filtered CuKα (λ = 1.5418) radiation. These data were assigned individual sigma values proportional to the estimated uncertainty of the visual intensity estimation (5), and were scaled and merged using overlapping diffractometer data (on the basis of structure factors).

Since 73 parameters were involved in the refinement of all non-hydrogen atoms with isotropic thermal factors, and refinement with anisotropic thermal corrections for the sulfur atom would require 78 parameters, the 303 observed reflections from the diffractometer data are not sufficient for a good refinement. The Weissenberg film data set provided 209 additional reflections that had been too weak to determine with the diffractometer. The combined data sets were used for the final refinements.

Scattering factors for neutral atoms were calculated from the analytical functions of Cromer and Waber (6). The sulfur scattering factor was corrected for real and imaginary anomalous dispersion using Cromer's (7) values. The real corrections were made separately for the two types of radiation used. A weighed average of the two different imaginary corrections (0.58 and 0.16 electrons) was used in the least squares. Neither data set was corrected for extinction. The linear absorption coefficient for MoKα is 2.3 cm^{-1} and the range of transmission factors for the crystal is 0.983 to 0.995; no absorption correction was made for the Mo reflections. For CuKα the linear absorption is 19.7 cm^{-1} and the range of transmission factors is from 0.803 to 0.959. An absorption correction was made for these data using the methods of Busing and Levy (8).

The structure was solved using Patterson and Fourier techniques (9). The heterocyclic sulfur and nitrogen atoms were located from analysis of the Patterson map and a three-dimensional Fourier map phased by these two atoms yielded the positions of the *o*-phenylene rings. Fourier and full matrix least squares refinement techniques with all atoms having isotropic temperature factors led to an unweighted residual $R_1 = (\Sigma \| Fo | - | Fc \|| / \Sigma | Fo |)$ of 0.083 and a weighted residual $R_2 = (\Sigma [\![w(| Fo | - | Fc |)^2 / \Sigma w | Fo |^2]\!])^{1/2}$, where $w = 1/\sigma(F)$ of 0.088. The function minimized in the least squares was $\Sigma w(| Fo | - | Fc |)^2$. When the sulfur atom was refined with anisotropic thermal parameters R_1 became 0.078 and R_2 became 0.084, a significant improvement according to the R ratio test (10).

In the final cycle of least squares no positional or

TABLE II

Final Anisotropic Thermal Parameters for S in $C_{12}H_8SNC_2H_4CN$

The thermal correction was of the form $\exp-(\beta_{11}h^2 + \beta_{22}k^2 + \beta_{33}l^2 + 2\beta_{12}hk + 2\beta_{13}hl + 2\beta_{23}kl)$.

A. Beta Values	$\beta_{11} \times 10^4$	$\beta_{22} \times 10^4$	$\beta_{33} \times 10^4$	$\beta_{12} \times 10^4$	$\beta_{13} \times 10^4$	$\beta_{23} \times 10^4$
S	374(13)	53(2)	76(3)	-11(5)	-6(6)	-1(3)

B. Root-Mean-Square Amplitudes of Vibration (Å) Along the Principal Axes of the Ellipsoid.

S	Major	Intermediate	Minor
	0.29	0.25	0.23

thermal parameter shifted more than 0.03 sigma. The final $\Delta F/\sigma$ values showed no apparent dependence on θ, F values, or origin of data; it thus appeared the weighting scheme was reasonable. The data merge appears to be satisfactory since the standard deviation of observation of unit weight for the 303 diffractometer reflections was 0.77 and for the film data 0.88. There were no positional differences of over 1σ in comparing the least squares refinement of the diffractometer-only data to that of the combined set. A final difference Fourier over the asymmetric unit showed no peak height greater than 0.40 $e^-/Å^3$, which is 8% of the height of an average carbon atom peak on the final Fourier map. The map did not reveal all of the hydrogen atoms so positions were calculated for those not located. In the last cycle of least squares the H atoms were used for structure factor calculation but were not refined. Table I contains the final positional and isotropic thermal parameters and Table II contains the anisotropic parameters for the sulfur atom.

Discussion.

Figure 1a is a labelled ORTEP drawing of the $C_{12}H_8SNC_2H_4CN$ molecule, and Figure 1b shows the dihedral angle of 135.3° formed by the two C_6H_4SN planes. The displacements of the atoms from the planes of the two phenylene rings are given in Table III and intraatomic distances and angles are given in Table IV.

A comparison of the bond distances and angles in the heterocyclic system of phenothiazine-10-propionic acid (1) and phenothiazine-10-propionitrile is given in Table V. Bond lengths in these chemically similar molecules are the same within experimental errors, and the small differences in the bond angles involving the S and N atoms are in all cases less than 3σ. These distances and angles were compared with other phenothiazine structures in our report of the structure of the propionic acid derivative (1).

A comparison of the various structural features of substituted phenothiazine molecules (1) shows the dihedral angle formed by the two C_6H_4SN moieties is the parameter which varies by the greatest amount from one derivative to the next. For six simple *N*-substituted phenothiazine molecules, including the present structure, the dihedral angles varies from 141.8 to 135.4, which is about 20 standard deviations for this parameter, while no other one bond distance or bond angle varies more than a few standard deviations. Our studies of similar heterocyclics involving arsenic, the phenoxarsine series, has also shown that the dihedral angles in these molecules are easily changes by substitution on the ring system, and that the dihedral angle changes between derivatives can be on the order of 10-20 degrees when no one bond distance or bond angle is changed by more than 0.02Å or 2.0°, respectively.

As an illustration of this, if the structure of the present report was to be planar instead of having a dihedral angles of 135.4° (a change of 45°) it would be possible to achieve planarity by a change of only 3σ in each of the central ring bond distance and angles (about 0.06Å for each bond and 2.5° for each angle).

TABLE III

Distances from the Least Squares Planes in $C_{12}H_8SNC_2H_4CN$

S,N,C(1)-C(6) Plane		S,N,C(7)-C(12) Plane	
S	-0.002(4)	S	-0.002(4)
N(1)	0.01(1)	N(1)	-0.01(1)
C(1)	0.01(1)	C(7)	0.03(1)
C(2)	-0.01(1)	C(8)	0.02(1)
C(3)	0.02(1)	C(9)	0.03(1)
C(4)	0.01(1)	C(10)	0.00(2)
C(5)	0.03(2)	C(11)	-0.03(1)
C(6)	-0.05(1)	C(12)	-0.01(2)
$x^2 = 17.5$		$x^2 = 14.0$	

Dihedral Angle = 135.4(3)°

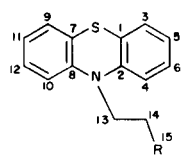
TABLE IV

Bond Distances and Bond Angles for $C_{12}H_8SNC_2H_4CN$

Bond Distances, Å		Bond Angles, deg.	
S-C(1)	1.77(1)	C(1)-S-C(7)	98.7(7)
S-C(7)	1.75(2)	C(2)-N(1)-C(8)	118.1(9)
N(1)-C(2)	1.43(2)	C(2)-N(1)-C(13)	118.5(9)
N(1)-C(8)	1.41(2)	C(8)-N(1)-C(13)	118(1)
N(1)-C(13)	1.48(2)	S-C(1)-C(2)	118.0(8)
N(2)-C(15)	1.15(2)	S-C(7)-C(8)	120.2(7)
C(1)-C(2)	1.42(2)	N(1)-C(2)-C(1)	118.6(8)
C(2)-C(4)	1.44(2)	N(1)-C(8)-C(7)	117(1)
C(4)-C(6)	1.42(2)	N(1)-C(13)-C(14)	112.5(8)
C(5)-C(6)	1.38(2)	N(2)-C(15)-C(14)	178(2)
C(3)-C(5)	1.39(2)	C(2)-C(1)-C(3)	122(1)
C(1)-C(3)	1.41(2)	C(1)-C(3)-C(5)	119(1)
C(7)-C(8)	1.43(2)	C(3)-C(5)-C(6)	121(1)
C(8)-C(10)	1.42(2)	C(5)-C(6)-C(4)	122(1)
C(10)-C(12)	1.36(3)	C(6)-C(4)-C(2)	118(1)
C(11)-C(12)	1.30(2)	C(4)-C(2)-C(1)	118.3(9)
C(9)-C(11)	1.43(2)	C(8)-C(7)-C(9)	119.3(8)
C(7)-C(9)	1.43(2)	C(7)-C(9)-C(11)	115(1)
wtd. ave. of 12 ring		C(9)-C(11)-C(12)	124(1)
C-C, with RMS dev. 1.40(1)		C(11)-C(12)-C(10)	124(2)
C(13)-C(14)	1.53(2)	C(12)-C(10)-C(8)	117(1)
C(14)-C(15)	1.48(2)	C(13)-C(14)-C(15)	112(1)

TABLE V

Comparison of the Distances and Angles of Phenothiazine-10-propionic Acid and Phenothiazine-10-propionitrile



	$C_{12}H_8SNC_2H_4COOH$	$C_{12}H_8SNC_2H_4CN$
C-S av.	1.77(2)Å	1.76(1)Å
C-N av. (ring)	1.43(2)Å	1.42(1)Å
C(13)-N	1.47(2)Å	1.48(2)Å
C-C av. (ring)	1.39(3)Å	1.40(1)Å
C(7)-S-C(1)	98.5(7)°	98.7(7)°
C(8)-N-C(2)	115.4(11)°	118.1(9)°
C(1)-C(2)-N	119.6(7)°	118.6(8)°
C(7)-C(8)-N	119.3(7)°	116.6(13)°
C(2)-C(1)-S	119.7(6)°	118.0(8)°
C(8)-C(7)-S	117.5(10)°	120.2(7)°
C(14)-C(13)-N	112.4(8)°	112.5(8)°
S,N-C(13)	162.5(8)°	161.6(8)°
C(1-6)SN-C(7-12)SN Dihedral Angle	136.0(3)° (a)	135.4(3)°

(a) These values are derived from the best planes obtained using weights for each atom proportional to the reciprocal of the squares of the positional sigmas perpendicular to the plane. Previous values used unit weights for all atoms of the plane.

The main concern with an emphasis of these dihedral angles as measures of electronic affects on the heterocyclic system is the question of the dependence of these angles on the solid state packing. It is to this point that this present structure is most valuable, in that the comparison of the propionic acid and propionitrile structures match two molecules which have nearly identical heterocyclic frameworks yet are completely different in their crystal packing (Figure 2). The acid derivative is characterized by strong hydrogen bonding which effectively dimerizes the molecules, and these dimers pack in the fashion shown in Figure 2a. The packing of the nitrile derivative is shown in Figure 2b. In both structures the only intermolecular contacts shorten than the corresponding van der Waals distances are C-H contacts in the range of 2.5-3.0Å. In the acid derivative seven of these intermolecular C-H close contacts act so as to increase the dihedral angle, and four act to reduce this angle. In the nitrile molecule two such contacts would tend to increase the dihedral angle, and eight would reduce it. In spite of these differences, the dihedral angles are the same within experimental error. We take this as evidence that the dihedral angles of these molecules is more easily distorted by electronic perturbations encountered in substitutions than by crystal packing.

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