Structural Studies of 2-Phenylthiazolidine

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Abstract

The crystal structure of 2-phenylthiazolidine ($C_9H_{11}NS$, $M_r = 165 \cdot 24$) was solved by direct methods using three-dimensional X-ray diffraction data. The structure at 293 K is orthorhombic, space group $P2_12_12_1$ with $a = 18 \cdot 148$ (9), $b = 8 \cdot 397$ (3), $c = 5 \cdot 627$ (3) Å, $V = 857 \cdot 5$ Å^3, $Z = 4$, $D_x = 1 \cdot 27$ Mg m^{-3}, Mo $K\bar{\alpha}$, $\lambda = 0 \cdot 7107$ Å, $\mu = 0 \cdot 263$ mm^{-1}, $F(000) = 352$, $R = 0 \cdot 086$ for 879 reflections with $I > 3\sigma(I)$. Only one H atom has been located from a difference synthesis. At 132 K, $R = 0 \cdot 027$ for 1881 reflections with $I > 3\sigma(I)$ recorded with the same crystal. No phase transition was observed, $a = 18 \cdot 013$ (3), $b = 8 \cdot 299$ (2), $c = 5 \cdot 577$ (1) Å, $V = 833 \cdot 7$ Å^3, $D_x = 1 \cdot 31$ Mg m^{-3}. All the H atoms were found on a difference map with this low-temperature data. A rigid-body thermal-motion analysis revealed a large libration of the molecule around the smallest axis of inertia at 293 K, which decreases strongly at low temperature. Structural results agree with ^{1}H NMR studies in solution. Charge-density deformation maps exhibit unidentified peaks near the S atom.

Introduction

Thiazolidines are important heterocyclic systems in biology and medicine. They constitute the backbone of the penicillin structure and are formed *in vivo* from cysteine and endogenous aldehydes.

Very few papers report crystal structures of thiazolidines, and only the 4-carboxylate derivatives have received attention. These derivatives have been shown to exist in amino acid or zwitterionic forms according to the other substituents of the ring. (*S*)-Thiazolidine-4-carboxylic acid (Goodman, Chen, Benedetti, Pedone & Corradani, 1972; Loscalzo, Kallen & Voet, 1973) adopts a zwitterionic form where the conformation of the thiazolidine ring is an envelope with S at the summit. An example of the amino acid form was found by Howard-Lock, Lock & Smalley (1985) in the structure of (*S*)-2,2,5,5-tetramethylthiazolidine-4-carboxylic acid.

We have investigated a great number of thiazolidine derivatives by NMR spectroscopy; one of them, 2-phenylthiazolidine, known for its radioprotective properties, gave a suitable crystal for X-ray study.

Experimental

Synthesis

2-Phenylthiazolidine was obtained by condensation of 2-aminoethanethiol hydrochloride and an excess of benzaldehyde with a suitable alkaline treatment, according to Schmolka & Spoerri (1957).

Data collection, structure solution and refinement

A plate-like crystal of dimensions $0 \cdot 15 \times 0 \cdot 3 \times 0 \cdot 5$ mm was sealed in a Lindemann capillary for the X-ray study. Accurate cell dimensions from 25 reflections with $20 \le \theta \le 27°$ and intensities of Bragg reflections were measured by an automatic four-circle diffractometer (Philips PW 1100) in the ω–2θ mode using Mo $K\alpha$ radiation. Two data sets at 293(2) and 132(0·5) K were recorded using similar ω–2θ scans, where the scan width was fixed to 1·3°, scan speed = $0 \cdot 015°$ min^{-1}.

2208 intensities up to $(\sin \theta)/\lambda < 0 \cdot 807$ Å^{-1} ($0 \le h \le 28$, $0 \le k \le 13$, $0 \le l \le 9$) were recorded at room temperature and 2114 intensities up to $(\sin \theta)/\lambda < 0 \cdot 807$ Å^{-1} ($0 \le h \le 28$, $0 \le k \le 13$, $0 \le l \le 9$) were collected at low temperature. Three standard intensities monitored at intervals of 2 h showed no significant variation. Both data sets were corrected for Lorentz and polarization factors, but no absorption and extinction corrections were made. 879 reflections with $I > 3\sigma(I)$ in the high-temperature data set and 1881 reflections with $I > 3\sigma(I)$ in the low-temperature data set.

The unit cell was found to be orthorhombic, space group $P2_12_12_1$ with four molecules situated at general positions. The structure was solved by direct methods (*MULTAN*; Germain, Main & Woolfson, 1971) using 499 reflections of the high-temperature data set with normalized structure factors $E \ge 1 \cdot 236$. Only one

Table 1. *Atomic coordinates* ($\times 10^5$, $\times 10^3$ *for* H) *and equivalent isotropic thermal parameters* ($\mathring{A}^2 \times 10^2$) *at 132 K*

$$U_{eq} = \tfrac{1}{3}\sum_i\sum_j U_{ij}a_i^*a_j^*\mathbf{a}_i \cdot \mathbf{a}_j.$$

	x	y	z	U_{eq}
S	71661 (2)	12470 (5)	12661 (8)	15 (1)
N	76255 (7)	39080 (16)	35467 (28)	16 (1)
C(2)	70691 (9)	26581 (18)	38885 (34)	15 (1)
C(4)	83066 (9)	30865 (21)	27470 (35)	18 (1)
C(11)	58785 (9)	28969 (20)	61772 (36)	18 (1)
C(10)	51655 (9)	35153 (23)	64837 (36)	21 (2)
C(6)	62874 (8)	32865 (18)	41406 (30)	14 (1)
C(7)	59782 (10)	42987 (23)	24204 (34)	24 (1)
C(5)	81143 (10)	19219 (22)	6757 (37)	21 (2)
C(9)	48629 (9)	45374 (22)	47874 (80)	22 (1)
C(8)	52700 (10)	49325 (24)	27510 (37)	27 (2)
H(C2)	716 (1)	195 (2)	533 (4)	36 (5)
H(N)	750 (1)	458 (2)	252 (3)	27 (6)
H(C5)	817 (1)	250 (2)	−86 (4)	24 (6)
H'(C5)	851 (1)	92 (2)	61 (3)	38 (6)
H(C4)	871 (1)	390 (2)	236 (3)	19 (5)
H'(C4)	854 (1)	244 (2)	418 (3)	24 (5)
H(C7)	622 (1)	452 (2)	108 (3)	24 (5)
H(C8)	508 (1)	564 (2)	156 (3)	27 (5)
H(C9)	436 (1)	496 (2)	492 (3)	15 (4)
H(C10)	490 (1)	326 (2)	799 (4)	40 (7)
H(C11)	608 (1)	221 (2)	732 (3)	29 (6)

H atom was located from this set of data, and the final $wR = 0.087\%$ for the 879 reflections above $3\sigma(I)$ (Sheldrick, 1976). All the H atoms were found for the low-temperature data set, using 1881 intensities above $3\sigma(I)$; $wR = 0.023\%$. Positions and isotropic Debye–Waller factors of the H atoms were refined. Unit weights were used for the high-temperature data set while for the low-temperature data w is defined as $1/\sigma^2(F_o)$ were $\sigma^2(F_o) = \sigma^2_{counting} + (0.02\ F_o^2)^2$.

Scattering factors for S, C and N were taken from *International Tables for X-ray Crystallography* (1974) while the factors for H were those of Stewart, Davidson & Simpson (1965). The absolute values of peaks and troughs in the final difference Fourier maps are respectively 0.3, $0.2\ e\ \mathring{A}^{-3}$ for the low-temperature data set and 0.4 and $0.5\ e\ \mathring{A}^{-3}$ for the high-temperature data. $(\Delta/\sigma)_{max}$ are respectively 0.2 and 0.005 for the high- and low-temperature structures; the atom positions corresponding to the best R values of the low-temperature structure are listed in Table 1.* Table 2 gives bond lengths and angles.

Thermal vibration analysis

Thermal motions of S, C, N were described by anisotropic parameters while isotropic ones were assigned to the H atoms. Fig. 1 shows the thermal

Table 2. *Bond lengths* ($\mathring{A}$) *and bond angles* (°) *with e.s.d.'s in parentheses*

S–C(2)	1·882 (2)	N–H(N)	0·830 (18)
S–C(5)	1·827 (2)	C(2)–H(C2)	1·011 (18)
N–C(2)	1·454 (2)	C(4)–H(C4)	1·032 (15)
N–C(4)	1·472 (2)	C(4)–H'(C4)	1·048 (18)
C(2)–C(6)	1·508 (2)	C(11)–H(C11)	0·926 (18)
C(4)–C(5)	1·545 (3)	C(10)–H(C10)	0·986 (20)
C(11)–C(10)	1·393 (2)	C(7)–H(C7)	0·886 (18)
C(11)–C(6)	1·392 (2)	C(5)–H(C5)	0·987 (20)
C(10)–C(9)	1·382 (4)	C(5)–H'(C5)	1·101 (15)
C(6)–C(7)	1·391 (2)	C(9)–H(C9)	0·972 (14)
C(7)–C(8)	1·392 (3)	C(8)–H(C8)	0·949 (18)
C(9)–C(8)	1·391 (4)		
C(2)–S–C(5)	92·1 (1)	C(11)–C(10)–H(C10)	118·1 (11)
C(2)–N–C(4)	106·5 (1)	C(9)–C(10)–H(C10)	121·4 (11)
C(2)–N–H(N)	112·6 (12)	C(2)–C(6)–C(11)	119·3 (1)
C(4)–N–H(N)	109·0 (12)	C(2)–C(6)–C(7)	121·2 (1)
S–C(2)–N	106·1 (1)	C(11)–C(6)–C(7)	119·4 (2)
S–C(2)–C(6)	112·0 (1)	C(6)–C(7)–C(8)	120·2 (2)
S–C(2)–H(C2)	103·8 (10)	C(6)–C(7)–H(C7)	120·7 (11)
N–C(2)–C(6)	114·1 (1)	C(8)–C(7)–H(C7)	119·1 (11)
N–C(2)–H(C2)	114·0 (10)	S–C(5)–C(4)	105·4 (1)
C(6)–C(2)–H(C2)	106·4 (10)	S–C(5)–H(C5)	113·4 (10)
N–C(4)–C(5)	109·2 (1)	S–C(5)–H'(C5)	112·5 (9)
N–C(4)–H(C4)	111·3 (9)	C(4)–C(5)–H(C5)	109·1 (10)
N–C(4)–H'(C4)	109·9 (9)	C(4)–C(5)–H'(C5)	110·8 (9)
C(5)–C(4)–H(C4)	114·6 (9)	H(C5)–C(5)–H'(C5)	105·7 (14)
C(5)–C(4)–H'(C4)	109·9 (9)	C(10)–C(9)–C(8)	119·7 (2)
H(C4)–C(4)–H'(C4)	101·7 (13)	C(10)–C(9)–H(C9)	122·4 (9)
C(10)–C(11)–C(6)	120·1 (2)	C(8)–C(9)–H(C9)	117·8 (9)
C(10)–C(11)–H(C11)	120·3 (11)	C(7)–C(8)–C(9)	120·1 (2)
C(6)–C(11)–H(C11)	119·6 (11)	C(7)–C(8)–H(C8)	118·4 (10)
C(11)–C(10)–C(9)	120·3 (2)	C(9)–C(8)–H(C8)	121·4 (10)

ellipsoids of the atoms of 2-phenylthiazolidine at low and high temperatures. **T**, **L** and **S** tensors describing the thermal motion of the molecule were fitted to the U_{ij}'s of the S, C and N atoms using the least-squares procedure proposed by Schomaker & Trueblood (1968). The elements of these tensors are given in Table 3. The r.m.s. differences between observed U_{ij} and those calculated from **TLS** tensors do not exceed $0.0016\ \mathring{A}^2$ (e.s.d. $= 0.0019$) in the low-temperature state. The estimated precision of the U_{ij} from the least-squares refinement is about $0.0008\ \mathring{A}^2$, so there are still significant non-rigid-body motions in the molecule even at 132 K.

The eigenvalues of **T** represent an isotropic translation of the whole molecule, the motion being halved
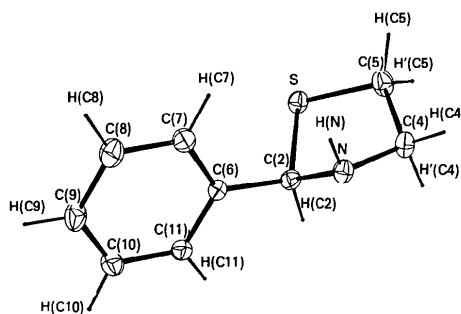

Fig. 1. Perspective view and numbering of the molecule: low-temperature state.

Table 3. *Rigid-body vibration parameters for all the heavy atoms of the molecule*

	Low temperature			High temperature		
$T (A^2 \times 10^{-4})$	165 (6)	1 (6)	−14 (6)	337 (20)	−8 (21)	−23 (21)
		152 (12)	22 (8)		273 (33)	27 (27)
			136 (10)			327 (32)
$L (rad^2 \times 10^{-4})$	30 (7)	1 (3)	−5 (3)	105 (24)	−18 (9)	−26 (9)
		13 (2)	7 (8)		32 (6)	24 (5)
			10 (2)			35 (6)
$S (Å \, rad \times 10^{-5})$	76 (55)	52 (35)	73 (38)	167 (183)	52 (116)	205 (126)
	− 34 (23)	−46 (31)	0 (17)	−166 (76)	−94 (103)	118 (57)
	− 42 (25)	−96 (17)	−30 (189)	−61 (82)	−207 (56)	−72 (628)
R.m.s. U(obs.) − U(calc.) ($Å^2$)	0·0016			0·0052		
E.s.d. U_j(obs.) ($Å^2$)	0·0019			0·0063		

Table 4. *T and L referred to the inertial axes of the molecule*

		Principal axes							Inertial	Direction cosine		
	$(Å^2 \times 10^{-4})$	$T (Å^2 \times 10^{-4})$			(°)	$L (rad^2 \times 10^4)$			moment	x	y	z
Low temperature	135	173	−5	−7	9·7	30	3	−1	43	0·890	−0·315	−0·328
	159		159	−6	4·2		19	−1	202	0·449	0·732	0·513
	115			117	3·1			3	209	0·078	−0·604	0·792
High temperature	363	357	−3	−22	34·5	105	2	−4	43	0·890	−0·318	−0·324
	308		299	22	10·6		42	4	201	0·449	0·724	0·522
	257			272	11·3			10	208	0·069	−0·611	0·788

at 132 K; also, there is a threefold difference between the libration motions of the molecule at room temperature and at 132 K. In Table 4 the quantities T and L are referred to the inertial axes of the molecule. At both temperatures the off-diagonal elements of the libration tensor L are quite small and it can be assumed that the molecule librates around the inertial axes.

The largest amplitude of vibration (5·8°) at high temperature is around the axis with the smallest moment of inertia, the electronic density near the H atoms being strongly smeared by these libration motions and only the HC(9) atom close to the axis with the smallest moment of inertia was localized on a difference map.

Discussion

Molecular geometry

The bond lengths and bond angles of the molecules are reported in Table 2. Fig. 2(a) illustrates a comparison of the bond lengths and angles of the thiazolidine ring found in our study with the values described by Howard-Lock *et al.* (1985) in 2,2,5,5-tetramethylthiazolidine-4-carboxylic acid. Bond angles and bond lengths are pretty close although the average C–S distance is larger. The lengthening of the C–S bond claimed by Howard-Lock *et al.* with respect to the results found in thiazolidine-4-carboxylic acid (mean value 1·799 Å) (Loscalzo *et al.*, 1973) is probably not caused by the steric requirements of the methyl groups. The compound described by Howard-Lock *et al.* can best be pictured by a plane through C(5)–S–C(2), with N and C(4) atoms twisted out of the plane on opposite sides at 0·382 (4) and

−0·269 (5) Å (half-chair conformation). In contrast, 2-phenylthiazolidine has an envelope conformation at 132 K with the N atom 0·596 Å out of the plane formed by C(2)–S–C(5)–C(4). The phenyl substituent is equatorial and perpendicular to the mean plane of the heterocyclic ring.
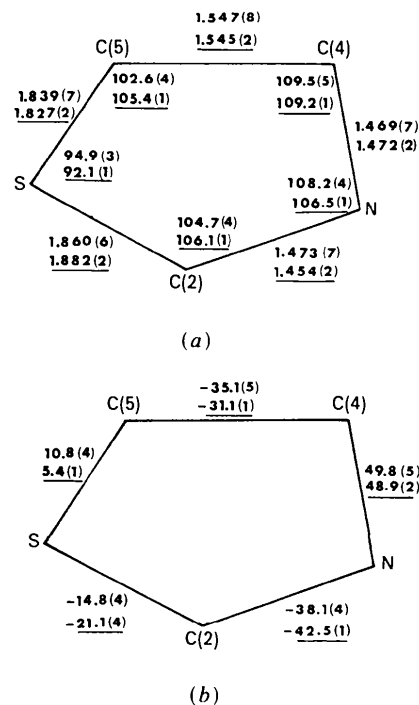

(a)

(b)

Fig. 2. Comparison of the conformations of the thiazolidine ring observed in (S)-2,2,5,5-tetramethylthiazolidine-4-carboxylic acid and 2-phenylthiazolidine: (a) bond lengths (Å), valence angles (°); (b) torsional angles (°). The underscored values refer to this study.

2-Phenylthiazolidine was also analyzed in solution by ^{1}H NMR spectroscopy. The H(4)/H(5) part of the 400 MHz spectrum was first solved by hand and then by computer simulation. A structural analysis was attempted by Terol, Subra, Fernandez, Robbe, Chapat & Granger (1981) with LIS reagents but their shifts and couplings did not reproduce the experimental spectrum. Contrary to their conclusions, we think that the *trans* coupling constants are the largest (8·06 Hz) and smallest (3·57 Hz) ones, and that the mean values (6·56 and 6·79 Hz) are *cis* coupling constants; this is corroborated by full analysis of the spectra of 4-phenylthiazolidine {J[H'(C4), H(C5)] = 8·86 Hz and J[H'(C4), H'(C5)] = 6·24 Hz} and of the more abundant isomer of 4-methyl-2-phenylthiazolidine {J[H'(C4), H(C5)] = 9·62 anJ J[H'(C4), H'(C5)] = 5·86 Hz} (Barbry, 1986). In this last compound, the substituents prefer the equatorial position (like the 2-phenyl substituent in 2-phenylthiazolidine): the large couplings between H(C2) and H(N) (13·5 Hz) and between H(N) and H(C4) (12·5 Hz) are typical of antiperiplanar atoms. So the H atom linked to the N atom is axial as shown in Figs. 1 and 3. Treatment of our coupling constants for 2-phenylthiazolidine with the Altona equation (Haasnoot, De Leeuw & Altona, 1980) leads to the following dihedral angles:

H(C4)–C(4)–C(5)–H(C5)	40·0°
H(C4)–C(4)–C(5)–H'(C5)	60·2°
H'(C4)–C(4)–C(5)–H'(C5)	41·3°

The values of *cis* dihedral angles of this compound in solution at 293 K are larger than those of the crystal (Fig. 3): 2-phenylthiazolidine appears to be conformationally less homogeneous in solution at room temperature than at 132 K in the solid state.
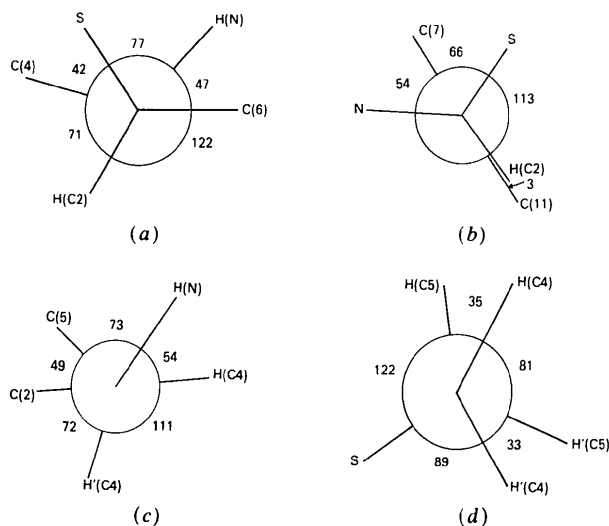
Molecular packing

Fig. 4 illustrates the packing of the molecules in the plane (110). No intermolecular distances are less than the sum of the van der Waals radii of the atoms involved except distance S–S (3·67 Å) which is just at the limit of the sum of the van der Waals radii. The four molecules in the cell are held together as a dimer by weak hydrogen bonds N–H(N) = 2·56 Å. The packing of the molecules can be described in terms of columns almost parallel to the **b** direction, each adjacent molecule being shifted by half a translation along the **z** direction. As shown in Fig. 4 each molecule is bound by van der Waals forces to six neighbouring molecules.

Difference electron density maps

Although our analysis was not undertaken with the intention of carrying out deformation density studies, the low R value encouraged us to believe that the deformation density might be of interest since studies of the thiazolidine ring had already been reported in the literature.

The difference Fourier syntheses were phased by final high-order parameters [(sin θ)/λ > 0·55 Å^{-1}] and calculated by means of the reflections of (sin θ)/λ < 0·80 Å^{-1}. The common scale factor was obtained from a least-squares refinement keeping the high-order parameters fixed.

Fig. 5(a) shows a section through the phenyl ring and contains the typical features, namely charge accumulation in the C–C bonds. The estimated e.s.d. at approximately 0·4 Å or further from the atom centre is 0·05 e Å^{-3}.

Fig. 5(b) shows a section through C(2)–S–C(5). Some density humps due to the bonding electrons are found, generally outside the interatomic vectors, as in (R)-thiazolidine-4-carboxylic acid (Kamo, Tanaka, Matsuura, Ashida & Kakudo, 1979). The lone-pair density of the N atom is also quite visible.

Around the S atom, see Fig. 5(c), two peaks are observed, the smallest one at more than 1 Å occupies the same position as that found by Kamo *et al.* (1979) and could represent the lone pair of the S in an sp^2

Fig. 3. Newman projections along (a) C(2)–N, (b) C(2)–C(6), (c) N–C(4) and (d) C(4)–C(5). Angles are given in ° ($\bar{\sigma}$ = 0·2°).
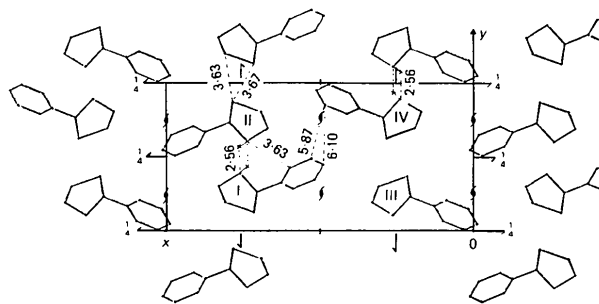

Fig. 4. Projection of the structure along c. The shortest distances (Å) between molecules are shown.

hybridization. However the near-95° angle between the peaks in the bonds S–C(5), S–C(2) and the summit S indicates that the $3p$ atomic orbitals of the S atom are very slightly hybridized with the $3s$ orbital, and consequently if we let the pure p_x, p_y orbitals be involved in the bonding, the p_z should contain the lone pair. This last conclusion has also been found by Cohen-Addad, Lehmann, Becker, Parkanyi & Kal-
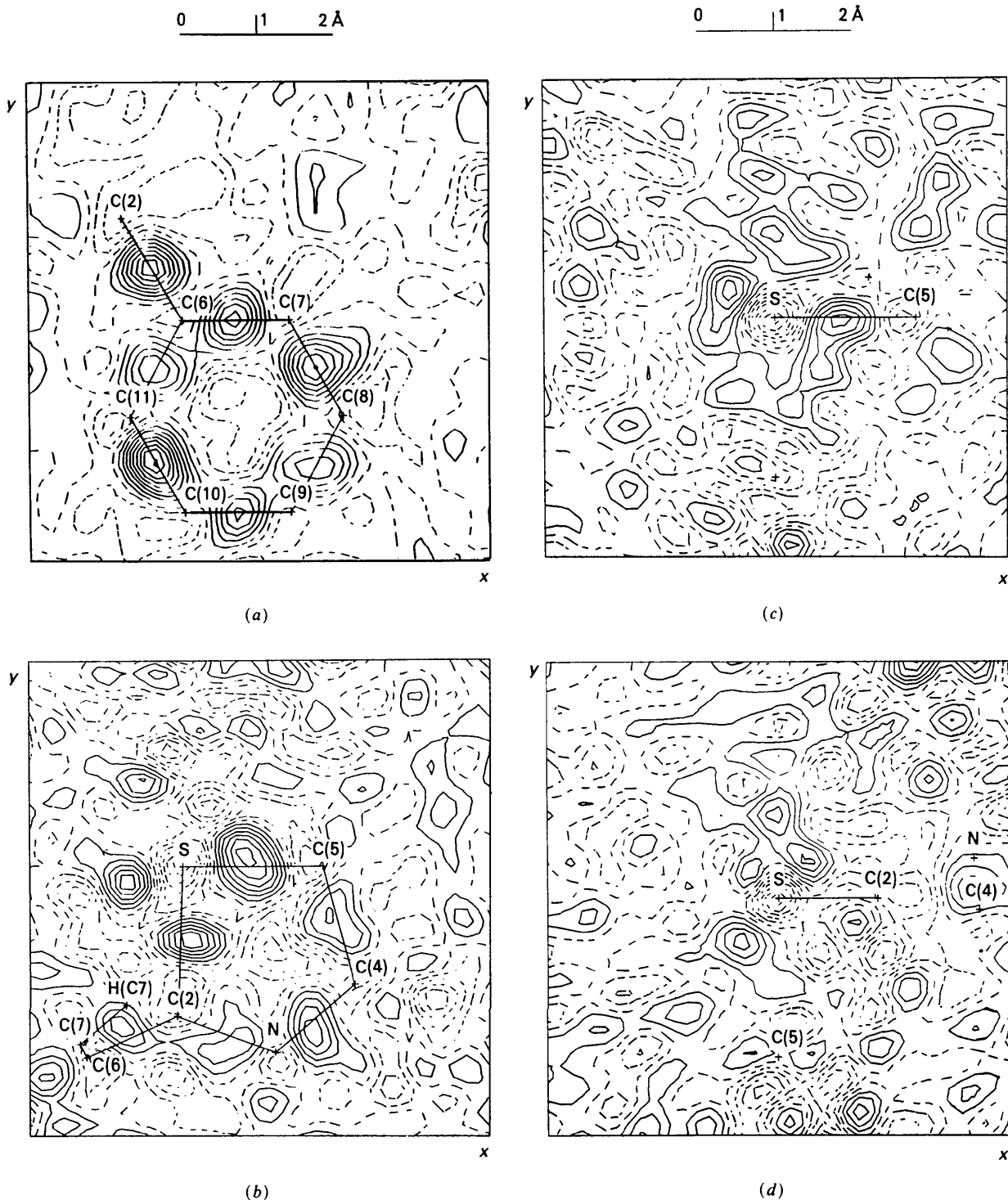

(a)

(c)

(b)

(d)

Fig. 5. Deformation density maps calculated in different planes of the molecule. Levels are 0.05 e Å^{-3}, negative and zero contours. (a) Plane of the phenyl ring, (b) C(5)–S–C(2) plane, (c) perpendicular to the C(5)–S–C(2) plane through the bond C(5)–S, (d) perpendicular to the C(5)–S–C(2) plane through the bond C(2)–S.

man (1984) (notice that the S atom is not in the same environment) but they could not explain it by modelling with an sp^2 deformation.

The difficulties of interpreting the results around the S show that more quantitative studies of this type are needed to elucidate the hybridization mode of the S atom where the d orbitals play an important role.

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