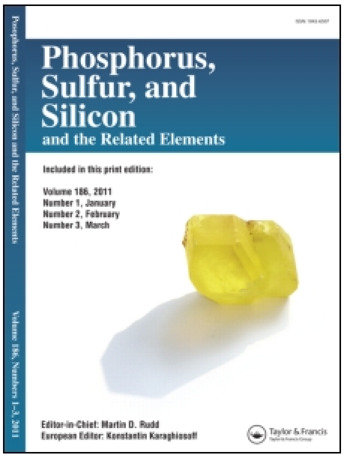

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

EFFECT OF CHALCOGEN SUBSTITUENTS (X=Se, S, O) ON MOLECULAR PROPERTIES OF 5-p-CHLOROBENZYLIDENE-3-METHYL-2-X-HYDANTOIN: X-RAY, PM-3 AND DATABASE STUDY

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To cite this Article Zesławska, E. , Oleksyn, B. J. , Korohoda, M. J. and Śliwiński, J.(1997) 'EFFECT OF CHALCOGEN SUBSTITUENTS (X=Se, S, O) ON MOLECULAR PROPERTIES OF 5-p-CHLOROBENZYLIDENE-3-METHYL-2-X-HYDANTOIN: X-RAY, PM-3 AND DATABASE STUDY', Phosphorus, Sulfur, and Silicon and the Related Elements, 126: 1, 111 — 124

To link to this Article: DOI: 10.1080/10426509708043550

URL: http://dx.doi.org/10.1080/10426509708043550

Phosphorus, Sulfur and Silicon, 1997, Vol. 126, pp. 111-124
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EFFECT OF CHALCOGEN SUBSTITUENTS (X = Se, S, O) ON MOLECULAR PROPERTIES OF 5-p-CHLOROBENZYLIDENE-3-METHYL-2-X-HYDANTOIN: X-RAY, PM-3 AND DATABASE STUDY

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(Received 12 December, 1996; In final form 21 January, 1997)

The X-ray structure analysis of a single crystal of 5-p-chlorobenzylidene-3-metyl-2-Se-hydantoin was carried out. It revealed that the molecule is a Z isomer with approximately planar conformation, the angle between the hydantoin and p-chlorophenyl planes being 4.2(1)°. The molecules form dimers linked by weak hydrogen bonds N-H$\cdots$ Se and C-H$\cdots$ Se about an inversion center. Semiempirical quantum mechanics calculations (PM-3) were performed for the three molecules of 5-p-chlorobenzylidene-3-methyl-2-X-hydantoin, where X = Se, S, O. Their results suggest that the planar conformation of these molecules is less energetically favourable than that with the planar molecular fragments significantly tilted to each other. Thus, the planar conformation which was found for many benzylidene derivatives in the crystalline state using Cambridge Structural Database System may be stabilized by intermolecular interactions. The net atomic charges and the bond lengths in the hydantoin ring are strongly affected by the X substituents. The electronegativity of X and the charge distribution in the hydantoin ring seem to be the most important factors in determining the anticonvulsant activity in the three compounds.

Keywords: hydantoin; crystal structure; hydrogen bonding; selenoorganic compounds

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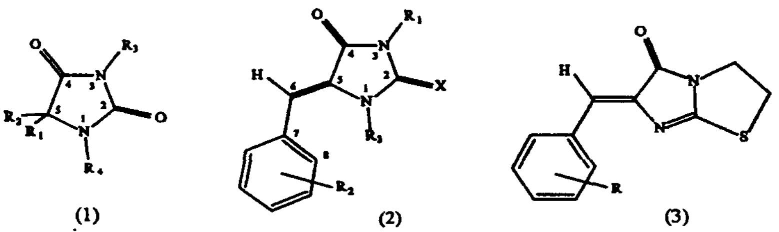
1. INTRODUCTION

Derivatives of hydantoin {(1) in Scheme 1} are interesting because of their biological activity. Especially important are the anticonvulsant compounds with one or two phenyl substituents (R_1, R_2) on C5 and methyl or ethyl substituents (R_3, R_4) on N1 and/or N3.



(1) (2) (3)

SCHEME 1

The relationship between the molecular structure and activity has been profoundly studied for phenytoin ($R_1 = R_2 = Ph$, $R_3 = R_4 = H$ in (1)) and its derivatives and vast literature of this subject has been accumulated[1,2]. Benzylidene derivatives (2) of hydantoin are less known, in particular those in which oxygen at position 2 is replaced by selenium atom (X = Se). Pharmacological studies on protection action against seizures after maximal electroshock (MES) and seizures produced by pentylenetetrazol (PTZ) were reported for (2) with X = (O, S, Se), R_1 = (Ph, C_6H_4-CH_3, CH_3, CH_2COOH), R_2 = (Cl, CH_3), R_3 = H[3, 4] and for (3) with R = (H, CH_3O, NO_2, Cl, Br).[5]

The crystal structure have only been determined for some of the abovementioned compounds [6–10].

In search for the relationship between the 3D-structure and anticonvulsant activity of the benzylidene derivatives of hydantoin we have undertaken investigations of the crystal and molecular structures of the compounds (2) with different substituents X and R_1, R_2= Cl.

In the present paper we concentrate on the molecular structure of the compounds (2), for which $R_1 = CH_3$, R_2 = p-Cl, R_3 = H, while X is Se (2i), S (2ii), or O (2iii). For (2i) the X-ray crystal structure analysis has been carried out, whereas the molecular geometry for all three compounds was studied with semiempirical (PM–3) quantum mechanics methods. The results of these studies, especially those concerning conformation, were compared to the experimental data for structurally similar compounds.found in the Cambridge Structural Database System.

2. EXPERIMENTAL SECTION

2.1. X-ray structure analysis

The synthesis of 5-p-chlorobenzylidene-3-methyl-2-selenohydantoin (2i) was described previously[11]. Yellow-orange single crystals were obtained from ethanol by slow evaporation. One of them, with dimensions 0,10 × 0.15 × 0.35 mm, was mounted on a KM-4 automatic single crystal diffractometer (KUMA Diffraction, Poland) which was used for the intensity data collection with MoKα radiation.

The lattice parameters and their standard deviations were determined by the least-squares analysis from the setting angles of 56 reflections, which were confined in the Θ range of 4 to 35 °. The intensities of 2807 reflections ($1° < \Theta < 25°$, $0 \leq h \leq 9$, $-2 \leq k \leq 12$, $-14 \leq l \leq 14$) were measured, from which 2083 considered as observed ($I > \sigma(I)$), while the number of unique reflections was 1901 (R(int) = 0.0475, R(sigma) = 0.0255).

Data reduction with corrections for Lorentz and polarization effects, but not for absorption, was performed using local KM–4 program.

The phase problem was solved by the direct methods using SHELXS–86[12] system of programs. The positions of hydrogen atoms were found on subsequent difference Fourier maps. Full-matrix least-squares refinement of atomic coordinates and anisotropic temperature parameters for non-hydrogen atoms was carried out, while for all hydrogens coordinates and isotropic temperature parameters were refined. To this end SHELXL-93[13] was used on F_o^2 with weighting scheme: $w^{-1} = \sigma^2(F_o^2) + (0.1P)^2 + 0.1\ P$, where $P = 1/3\ [\max(F_o^2, 0) + 2F_c^2]$.

The final values of the conventional discrepancy factor was R = 0.0397 for $F_o > 4\sigma(F_o)$ and 0.0410 for all 1901 unique reflections, goodness of fit S = 0.983, shift/σ in the last cycle 0.00, the largest difference peak, 0.74 eÅ^{-3}.

Crystal data: $C_{11}H_9ClN_2OSe$, FW = 299.6, triclinic, $P\bar{1}$, a = 6.6317(6) Å, b = 8.9173(10) Å, c = 10.3204(9) Å, α = 77.211(9)°, β = 79.294(7)°, γ = 81.618(7)°, V = 581.3 Å^3, Z = 2, D_m = 1.67(1) gcm^{-3}, D_x = 1.712 gcm^{-3}, μ(MoKα) = 3.44 mm^{-1}.*

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* Supplementary Material: Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. 101131 UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

2.2. Computational Details

Three molecules, (2i), (2ii) and (2iii), were constructed as Z isomers and low energy conformations were found using conformational search module of ChemPlus extention of HyperChem[14] molecular modeling system. These calculations were performed with semiempirical PM-3 method as the only one which contains parametrization for selenium.[15]

All calculations were carried out on PC 486 computer.

3. RESULTS AND DISCUSSION

3.1. Description of the structure of 5-p-chlorobenzylidene-3-methyl-2-Se-hydantoin (2i)

The final atomic coordinates of (2i) obtained as the result of X-ray structure analysis are listed in Table I, while the ORTEP[16] projection of the molecule together with its numbering scheme is given in Fig. 1. Interatomic distances and bond angles are collected in Table II.

TABLE I Fractional atomic coordinates and mean temperature factors U_{eq} (Å^2) for non-hydrogen atoms in molecule (2i) with e.s.d.s in parentheses.

	x/a	*y/b*	*z/c*	U_{eq}
N1	0.1689(5)	0.5210(4)	0.6785(3)	0.0445(7)
C2	0.2612(5)	0.6241(4)	0.5787(3)	0.0429(7)
Se1	0.18460(7)	0.70292(5)	0.41544(4)	0.0608(2)
N3	0.4295(4)	0.6601(3)	0.6200(3)	0.0433(6)
C13	0.5759(8)	0.7637(6)	0.5420(5)	0.0588(11)
C4	0.4467(6)	0.5782(4)	0.7499(4)	0.0440(7)
O1	0.5830(5)	0.5882(4)	0.8104(3)	0.0607(7)
C5	0.2721(5)	0.4862(4)	0.7903(3)	0.0418(7)
C6	0.2340(6)	0.3971(4)	0.9137(3)	0.0434(8)
C7	0.0751(5)	0.2982(4)	0.9780(3)	0.0401(7)
C8	−0.0982(6)	0.2863(5)	0.9229(4)	0.0501(9)
C9	−0.2419(7)	0.1889(5)	0.9896(4)	0.0554(10)
C10	−0.2186(6)	0.1005(4)	1.1138(4)	0.0474(8)
Cl1	−0.4020(2)	−0.0226(1)	1.1984(1)	0.0654(3)
C11	−0.0539(7)	0.1105(5)	1.1741(4)	0.0562(10)
C12	0.0918(6)	0.2081(5)	1.1069(4)	0.0501(9)

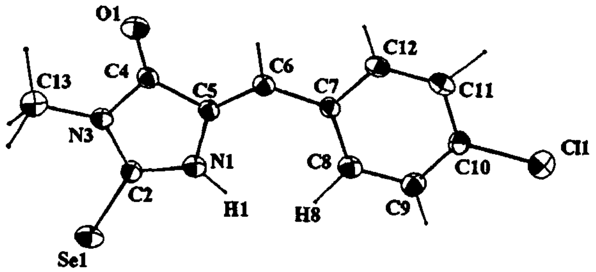

FIGURE 1 Atom numbering scheme of the molecule of 5-p-chlorobenzylidene-3-methyl-2-Se-hydantoin (2i)

TABLE II Bond lengths (Å) and angles (°) for non-hydrogen atoms in molecule (2i) with e.s.d.s in parentheses

N1-C2	1.338(5)	C4-O1	1.214(4)	C6-C7	1.443(5)
N1-C5	1.403(4)	C4-C5	1.460(5)	C7-C8	1.400(5)
C2-N3	1.369(4)	C5-C6	1.344(5)	C7-C12	1.408(5)
C2-Se1	1.811(3)	C8-C9	1.367(6)	C10-Cl1	1.737(4)
N3-C4	1.394(4)	C9-C10	1.370(5)	C11-C12	1.379(6)
N3-C13	1.444(5)	C10-C11	1.376(6)		

C2-N1-C5	111.4(3)	N1-C5-C4	104.7(3)
N1-C2-N3	108.0(3)	C5-C6-C7	132.9(3)
N1-C2- Se1	127.3(3)	C8-C7-C12	116.9(3)
N3-C2-Se1	124.7(3)	C8-C7-C6	125.0(3)
C2-N3-C4	110.4(3)	C12-C7-C6	118.2(3)
C2-N3-C13	126.4(3)	C9-C8-C7	121.6(3)
C4-N3-C13	123.2(3)	C10-C9-C8	120.0(4)
O1-C4-N3	123.9(3)	C11-C10-C9	120.9(4)
O1-C4-C5	130.5(3)	C11-C10-Cl1	119.3(3)
N3-C4-C5	105.5(3)	C9-C10-Cl1	119.8(3)
C6-C5-N1	133.2(3)	C10-C11-C12	119.3(3)
C6-C5-C4	122.0(3)	C11-C12-C7	121.4(3)

The selenium atom forms with C2 a bond of length 1.811(3) Å which is well comparable to that observed by Conde, Lopez-Castro and Marquez[17] in selenosemicarbazone, i.e. 1.83(2) Å. These authors classify this bond as having only partial double-bond character.

The bond lengths in p-chlorophenyl moiety are normal and those in the C5 = C6 – C7 linkage to the hydantoin ring are characteristic of the conjugated system $C_{sp^2} = C_{sp^2} - C_{Ar}$[18]. The large value ofthe C5 = C6–C7 bond angle, 132.9(3)°, is most probably caused by the steric repulsion between H1 and H8.

The bond lengths in the hydantoin rings are consistent with the charge distribution described below. The hydantoin fragment is planar with the distance of Se atom from the ring plane equal to 0.015 Å. The molecule is a Z isomer with approximately planar conformation, the torsion angle C5=C6-C7-C8 being −6.4(7)°. The planes of the hydantoin and p-chlorophenyl moieties form an angle of 4.2 (1)°.

The packing of molecules in the unit cell is shown in Fig. 2.

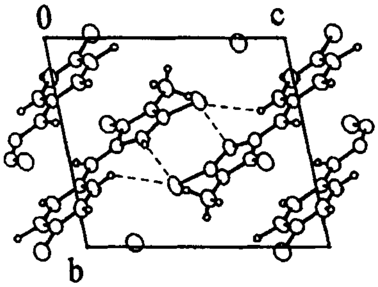

FIGURE 2 Packing of molecules in the unit cell of the crystalline 5-p-chlorobenzylidene-3- methyl-2-Se-hydantoin (2i) projected along X axis. Hydrogen bonds are denoted by broken lines

The pairs of the molecules related by the inversion centre in the position (0, 0.5, 0.5) form dimers with short contacts between selenium atom of one molecule and H1 and H8 atoms of the other. These contacts may be called weak hydrogen bonds, N1-H1··· Se1 and C8-H8··· Se1, with parameters given below.

D	A	D···A (Å)	D-H (Å)	H···A(Å)	D-H···A(°)
N1	Se1$^{i)}$	3.669(4)	0.89(6)	2.83(6)	158(2)
C8	Se1$^{i)}$	3.619(4)	1.08(4)	2.75(4)	138(2)

i): -x, -y+1, -z+1

The dimerization seems to stabilize the intramolecular distance H1··· H8 = 1,96(6) Å, which is much shorter than the sum of the van der Waals radii, 2.40 Å. Similar N-H···Se bonds between mutually centrosymmetric molecules of 2-formylpyridine selenosemicarbazone were observed by Conde, Lopez-Castro and Marquez.[17] The N··· Se distance in these bonds was 3.52 Å.

The shortest contacts between the dimers are formed by selenium and N3 (−x+1, −y+1, −z+1), O1 (−x+1, −y+1, −z+1) and Cl1 (x+1, y+1, z−1). The corresponding interatomic distances, 3.861(3), 3.837(3) and 3.971(1) Å, respectively, are longer than the sums of van der Waals radii of the relevant atoms.

3.2 Semiempirical calculations

In the molecules (2) only one possible rotation, around C6-C7 bond, can be considered. The torsion angle τ = C5-C6-C7-C8 has been chosen for conformational analysis. The conformers with the lowest total energy E_t found within this analysis are listed in Table III. Also heat of formation (H_f) values were calculated for each minimum.

TABLE III The results of conformational analysis for the compounds (2i), (2ii) and (2iii)

(2i)	*MIN1*	*MIN2*	*MIN3*	*MIN4*	*MIN5*	*MIN6*
τ(°)	-50.56	-28.40	28.18	50.56	-79.35	0.12
$E_t(\tau)$ (kcal/mol)	-59287.4	-59287.2	-59287.2	-59287.4	-59287.0	-59286.8
Heat of formation (kcal/mol)	16.04	15.73	16.34	16.17	16.83	19.11
(2ii)	*MIN1*	*MIN2*	*MIN3*	*MIN4*	*MIN5*	
τ(°)	99.21	-29.50	25.62	53.64	49.77	
$E_t(\tau)$ (kcal/mol)	-59074.27	-59074.52	-59074.50	-59074.54	-59074.65	
Heat of formation (kcal/mol)	26.70	26.24	25.89	25.92	25.90	
(2iii)	*MIN1*	*MIN2*	*MIN3*	*MIN4*	*MIN5*	
τ(°)	-57.23	-31.83	19.71	53.02	79.46	
$E_t(\tau)$ (kcal/mol)	-61578.79	-61578.78	-61578.19	-61578.95	-61578.66	
Heat of formation (kcal/mol)	-43.62	-41.62	-39.81	-43.61	-43.36	

The function $E_t(\tau)$ for compound (2i) revealed six minima with very similar energy among which the one closest to that observed in the crystal structure ($\tau = -6.4°$) corresponds to $\tau = 0.12°$. This minimum does not occur for the other two compounds, (2ii) and (2iii), for which the function $E_t(\tau)$ has five minima. The results of PM-3 optimization of these conformers are given in Table IV, together with heat of formation and dipole moment values.

The τ value of four minima (MIN1-MIN4) for (2i) were preserved by the optimization procedure with only slight changes, while the conformations for MIN5 and MIN6 appeared to be unstable and were transformed by optimization into MIN1 and MIN3, respectively. In the case of compounds (2ii) and (2iii) the optimization of MIN5, found by the conformational search (Table III), led to the conformation of MIN4. For the molecule (2ii) MIN1, given by the conformational analysis (Table III), has been significantly changed by the optimization ($\tau = -50.70°$, Table IV).

Comparison of the optimized conformations (Table IV) shows that for (2i) the minima are symmetrical in pairs: MIN1-MIN4, MIN2-MIN3. This symmetry is less conspicuous for corresponding pairs of minima for (2ii) and (2iii). A possible reason of this behaviour may be certain asymmetry in the electron density distribution, which seems to follow the replacement of the selenium atom by sulfur and oxygen.

TABLE IV Results of optimization of molecules (2i), (2ii), (2iii)

(2i)	*MIN1*	*MIN2*	*MIN3*	*MIN4*
torsion angle τ(°)	-51.50	-28.19	28.18	51.49
heat of formation (kcal/mol)	15.59	15.73	15.73	15.59
dipole moment (Debyes)	4.92	5.06	5.09	4.92
(2ii)	*MIN1*	*MIN2*	*MIN3*	*MIN4*
torsion angle τ(°)	-50.70	-30.58	30.57	57.01
heat of formation (kcal/mol)	25.44	25.57	25.57	25.55
dipole moment (Debyes)	3.58	3.73	3.73	3.60
(2iii)	*MIN1*	*MIN2*	*MIN3*	*MIN4*
torsion angle τ(°)	-60.91	-33.31	18.29	50.51
heat of formation (kcal/mol)	-43.65	-43.63	-43.05	-43.81
dipole moment (Debyes)	1.62	1.74	1.73	1.65

The heats of formation (H_f) corresponding to the four low-energy conformers of (2i), (2ii) and (2iii) differ only slightly among themselves (Table IV), but there is a very pronounced change in them when passing from selenium and sulfur compounds to their oxygen analogues, for which the H_f values are much lower. The calculated dipole moments decrease from 4.9 – 5.1 D, for the conformers of (2i), through 3.6 – 3.7 D for (2ii), to 1.6 - 1.7 D for (2iii).

The results of our calculations suggest that the planar structure of all three molecules, i.e. of selenium, sulfur and oxygen analogues, is less favourable than that with the ring fragments significantly tilted to each other. Thus, the almost flat molecule (2i) which occurs in the crystalline state seems to be stabilized by intermolecular interactions, especially by N1-H1··· Se1 and C8-H8··· Se1 hydrogen bonds, described above. Similar conclusion was drawn by Karolak-Wojciechowska and Kieć-Kononowicz[9] from their molecular mechanics calculations (MMX method) for the p-chloro-compounds of type (3). These calculations revealed shallow minima in the regions of $\tau = (-120°) - (-60°)$ and $(60°) - (120°)$, separated by a low saddle for $\tau = 0°$.

The calculations of net atomic charges for (2i), (2ii) and (2iii), illustrated in Fig. 3, show the following tendencies.

Among X substituents the oxygen atom in (2iii) is the most negative, while both sulfur in (2ii) and selenium in (2i) have similar, less negative charges. There is a systematic and significant change of charges on the hydantoin atoms C2, N1

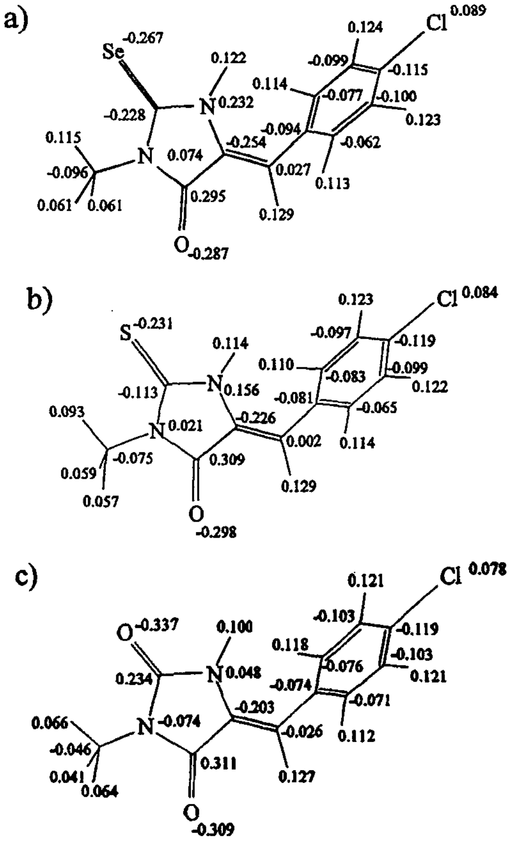

FIGURE 3 The net atomic charges calculated for a) molecule (2i), b) molecule (2ii), c) molecule (2iii)

and N3 when passing from (2i), through (2ii), to (2iii). The charges on C2 increase from negative to positive values while those on the nitrogen atoms decrease from positive to almost zero for N1 and from small positive to small negative for N3. The charges on C4, C5 and O atoms remain approximately constant.

A comparison of the selected bond lengths, bond angles and interplanar angles in Z isomers of six compounds of types (2) and (3) is given in Table V.

The influence of substituents X is most noticeable for the bond lengths which, in general, depend on the net atomic charges. For example, the N1-C2 bonds in (2i) and in compounds of type (3) are shorter than in compounds with X = O, where N1 and C2 atoms have opposite charges on N1 and C2. The tendencies of bond length changes which can be traced in Table V show that the calculated charges do not contradict the experimental results. This indicates that the Mulliken approximation, used in this case, has certain predictive value for changes in bond lengths.

TABLE V Comparison of selected bond lengths (Å), angles (°) and interplanar angles (°) for molecules of type 2 and 3 (isomers Z)

Molecule	*(2i)*	*(2) X = O,* $R_1 = R_3 = H$, $R_2 = p\text{–}OCH_3$	*(2) X) =O,* $R_1 = R_2 = H$, $R_3 = CH_3$	*(2) X =O,* $R_1 = H$, $R_3 = CH_3$, $R_2 = 2, 4, 6\text{–}CH_3$	*(3)* $R = p\text{–}Cl$	*(3)* $R = m\text{–}NO_2$
N1 - C2	1.338(5)	1.369(3)	1.355(3)	1.343(9)	1.294(6)	1.296(5)
C2 - N3	1.369(4)	1.369(5)	1.380(3)	1.372(9)	1.384(6)	1.389(5)
N3 - C4	1.394(4)	1.360(5)	1.360(3)	1.345(9)	1.370(5)	1.383(5)
C4 - C5	1.460(5)	1.468(5)	1.472(3)	1.464(10)	1.517(5)	1.500(6)
C5 - N1	1.403(4)	1.373(5)	1.404(3)	1.380(8)	1.413(5)	1.407(5)
C5 - C6	1.344(5)	1.328(6)	1.332(3)	1.299(9)	1.337(6)	1.334(5)
C6 - C7	1.443(5)	1.445(5)	1.446(3)	1.468(11)	1.459(5)	1.462(5)
C4 - O	1.214(4)	1.210(5)	1.220(3)	1.206(8)	1.215(5)	1.217(4)
N3 - R_1	1.444(5)	-	-	-	1.456(6)	1.455(5)
C2 - X	1.811(3)	1.203(5)	1.214(3)	1.219(8)	1.714(5)	1.722(4)
C2 - N1 - C5	111.4(3)	110.9(3)	110.5(2)	110.0(5)	104.2(4)	103.9(3)
N1 - C2 - N3	108.0(3)	106.8(3)	106.6(2)	107.6(6)	115.8(5)	116.3(4)
C2 - N3 - C4	110.4(3)	111.2(3)	112.6(2)	111.4(6)	108.6(4)	107.4(4)
N3 - C4 - C5	105.5(3)	105.7(3)	104.7(2)	105.1(6)	102.2(4)	102.6(4)
C4 - C5 - N1	104.7(3)	105.2(3)	105.5(2)	105.8(5)	109.2(4)	109.9(4)
interplanar angles *	4.3(3)	5.4(3)	45.9(3)	84.2(3)	~0.0	8.1(7)
references	this paper	6	7	8	9	10

* between planes of hydantoin and benzene rings

The bond angles for the compounds of type (2) seem to be less influenced by X. The angles in the molecules of type (3) are different, since their hydantoin moiety is combined with the thiazole ring. The shape of the compared molecules is most probably influenced by their packing in the crystals, because the less energetically favoured planar conformation is more frequent than the folded one (Table IV).

3.3 Database Study

In order to compare the results of our calculations with the conformations observed for structurally similar molecules in the crystalline state, the search for fragments consisting of a five-membered ring connected with a benzene ring *via* = CR-linkage has been done using Cambridge Structural Database System[19]. The numbering of atoms in the fragments is given in Fig. 4a. The fragments fulfilled the following criteria:

- the five-membered ring C2, A3 – A6 has only two specific substituents, i.e. doubly bound oxygen atom at A3 and/or at A6 and the benzylidene grouping (C1, C7-C12) with any substituents, A denotes carbon or any other atom;

- the benzylidene grouping occupies position α with respect to the carbonyl;
- the double benzylidene bond cannot be engaged in any fused ring system;
- the five-membered ring is not a part of any ferrocen-like or sandwich-like metal complex.

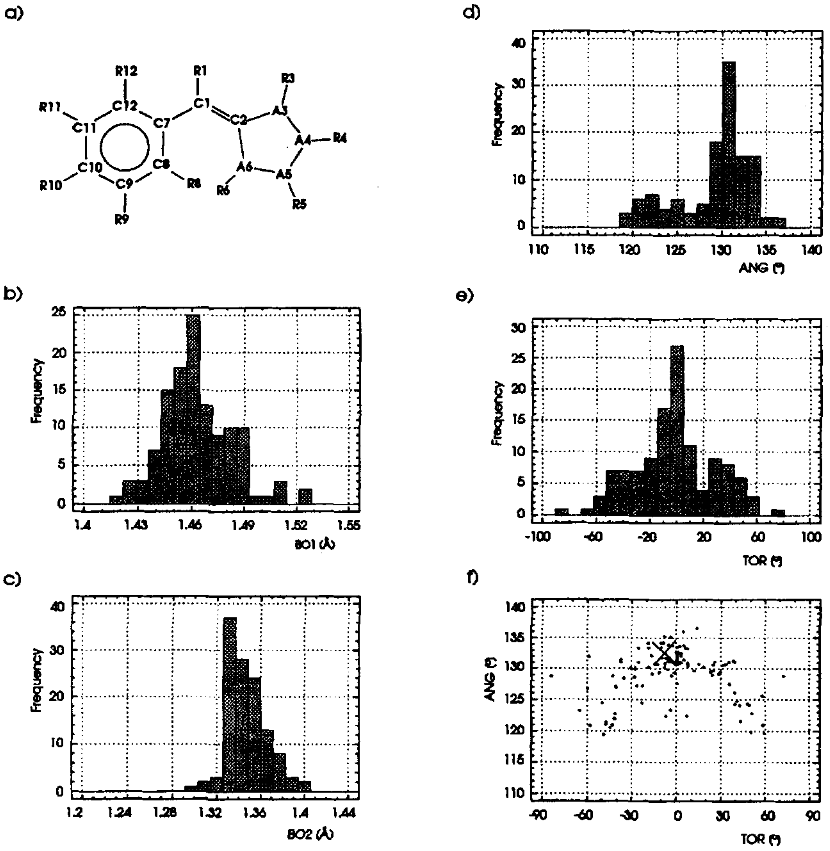

FIGURE 4 Statistical analysis of molecular fragments retrieved from Cambridge Structural Database. a. Numbering of atoms in fragments: A – carbon or any other atom; R1, R4, R5, R8-R12 - hydrogen or any other atom or group, R3 and/or R6 – oxygen atom. b. Frequency histogram for BO1 = C7–C1 bond lengths. c. Frequency histogram for BO2 = C1 = C2 bond lengths. d. Frequency histogram for ANG = C7–C1 = C2 bond angles. e. Frequency histogram for TOR = C8–C7–C1 = C2 torsion angles. f. Scatter plot of ANG vs TOR values, cross represents molecule (2i)

The number of fragments which satisfy these conditons is 121. They occur in structures whose reference codes are available from the authors. Statistical interpretation of the structural parameters for these structures was carried out with the use of Statgraphics Plus graphics system.[20] The histograms of the bond lengths, BO1 = C1–C7, BO2 = C1 = C2, bond angles, ANG = C7–C1 = C2, as well as the torsion angles TOR = C8–C7–C1=C2, are shown in Figs. 4b - 4e, respectively. The numbers were ascribed to the atoms in such a manner that $-90° \leq \text{TOR} \leq 90°$. Selected statistical parameters for the distributions of these variables are listed in Table VI.

TABLE VI Selected statistical parameters for BO1 = C7-C1, BO2 = C1 = C2, ANG = C7-C1=C2 and TOR = C8-C7-C1=C2 in 121 molecular fragments shown in Fig. 4a

Variable	*BO2(Å)*	*BO1(Å)*	*ANG(°)*	*TOR(°)*
standard deviation	0.017	0.020	4.10	29.86
minimum value	1.298	1.421	119.47	–83.94
maximum value	1.399	1.526	136.66	72.39
range	0.101	0.105	17.19	156.33

The mean values of BO2 and BO1 agree well with those established[18] as typical interatomic distances for conjugated double and single bond in the fragments $C_{sp^2} = C_{sp^2} - C_{Ar}$ which are: 1.339(11) Å and 1.470(6) Å, respectively.

The behaviour of the bond angles, ANG, is very interesting because it indicates a remarkable flexibility of these, relatively "hard" geometrical parameters. They change in a broad range of 17° and their frequency distribution (Fig. 4d) is bimodal with one lower maximum for 122° and the other, much higher, for 131°.

The torsion angles, TOR, change in broad range, (–84°) - (72°), and show greater dispersion of the frequency distribution than the bond lengths and bond angles. Their histogram (Fig. 4e) has a high maximum for TOR close to 0° and broad "wings" for ranges: (–20°) – (–90°) and (20°) – (90°).

The scatter plot of ANG *versus* TOR (Fig. 4f) shows quite distinctly that the bond angles are correlated to the torsion angles *via* function similar to that found by Hummel, Huml and Bürgi[21] for methoxy-phenyl grouping. The points in the plot tend to cluster along a bell-shape curve, with the greatest density around points of coordinates: TOR = 0°, ANG = 132°; TOR = –50°, ANG = 122°, and TOR = 50°, ANG = 122°. Inspection of the molecules corresponding to these best occupied areas of the plot shows that the first of them comprises mainly molecules with no bulky substituents in the vicinity of C7 and C1. Most of the molecules included in the other two areas have substituents, some of them quite bulky, most often on C1 and/or in α-positions with regard to C2.

The behaviour of the bond and torsion angles suggests that a compromise between the requirements of conjugation and of minimum substituent interactions is achieved by an interplay between these two molecular parameters. It seems that the process of crystallization "chooses" the less energetically preferred planar conformations as those favoured by packing forces. These conformations, for the molecules without bulky substituents, can be formed by opening of C2=C1–C7 angle which adopts values from the range of 128 to 139°. The above conclusion must be, however, verified by *ab initio* calculations which we plan to perform.

The position of the point representing molecule (2i) in the densely occupied upper part of the curve shows that both ANG and TOR values for this molecule are typical for the systems whose substituents in the vicinity of C1 have small van der Waals radii.

4. CONCLUSIONS

1. The molecule of 5-p-chlorobenzylidene-3-methyl-2-X-hydantoin in the crystalline state is Z isomer. It is approximately planar with the flat hydantoin ring. Its conformation seems to be determined by the molecular packing in the crystal, this packing being dominated by weak hydrogen bonds N-H···Se and C–H··· Se.
2. Semiempirical calculations for the molecules with X = Se, S, O show that the most energetically favoured conformations are those with C5=C6–C7–C8 angles, roughly, close to 60° and –60°.
3. Comparison of the calculated net charges in the molecules (2i), (2ii) and (2iii) and bond length values in six molecules shows that X substituents exert their influence most probably *via* changes of electron density distributions in the hydantoin ring, especially in vicinity of C2, N1 and N3.
4. The database study of molecular fragments structurally similar to the investigated compounds show that in the crystalline state bond angles in the C–C=C linkage and the torsion angles about its C–C bond are strongly correlated. The relationship between these angles implies that, whenever the substituents permit it, the planar conformation is adopted by the molecules with significant increase of the C–C=C bond angle.
5. In view of the anticonvulsant activity of the (2i), (2ii) and (2iii) compounds, which increases in the order: 0.0, 42.9, 72.0 (PTZ protection test[3]), it seems that the most important for this activity is the electronegativity of X substituent. The increase of the negative charges on the substituents Se, S, O leads to a systematic change of charges on C2 (increase) and N1 (decrease) which, in turn, may influence the reactivity of the hydantoin ring. The conformation, which only slightly depends on X, should not affect the activity.

Acknowledgements

This work was supported by the Polish State Committee for Science Research (KBN) under project No. P.303.184.03 and by Pedagogical University in Kraków under project BW/127/M/95 and BW/212/M/96.

The autors are grateful to dr Katarzyna Stadnicka for her guiding assistance in the diffractometric measurements and for discussion of the results as well as to dr Maria Ciechanowicz-Rutkowska for help in calculations with the use of ChemPlus.

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