The Molecular and Crystal Structure of *tert*-Butyl N^{α}-*tert*-Butoxycarbonyl-L-(*S*-trityl)cysteinate and the Conformation-Stabilizing Function of Weak Intermolecular Bonding

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The title compound, $C_{31}H_{37}NO_4S$ {systematic name: (*R*)-*tert*-butyl-2-[(*tert*-butoxycarbonyl)amino]-3-(tritylsulfanyl)propanoate} is an L-cysteine derivative with three functions: NH_2, COOH and SH, blocked by protecting groups *tert*-butoxycarbonyl, *tert*-butyl and trityl, respectively. The main chain of the molecule adopts the extended, nearly all-*trans* C_5 conformation with the intramolecular N–H···O=C hydrogen bond. The urethane group is not involved in any intermolecular hydrogen bonding. Only weak intermolecular hydrogen bonds and hydrophobic contacts are observed in the crystal structure. These are C–H···O hydrogen bonds and CH/π interactions with donor···acceptor distances, C···O *ca.* 3.5 Å and C···C *ca.* 3.7 Å, respectively. The first type of interaction links phenyl H-atoms and carbonyl groups. The second type of interaction is formed between a methyl group of the *tert*-butyl fragment and a trityl phenyl ring. The resulting molecular conformation in the crystal is very close to an *ab initio* minimum energy conformer of the isolated molecule. The extended C_5 conformation of the main peptide chain is the same and there is slight discrepancy in the disposition of trityl phenyl rings. Their small dislocation creates the possibility of forming the entire network above of extensive, specific, weak intermolecular interactions; these constrain the molecule and permit it to retain the minimum energy C_5 conformation of its main chain in the solid state. In contrast, in *n*-hexane solution, where such specific interactions cannot occur, only a small population of the molecules adopts the extended C_5 conformation.

Key words crystal structure; FTIR spectroscopy; *ab initio* calculations; C_5 conformation; weak hydrogen bonds; *S*-tritylcysteine

The solid-state structure of amino acid derivatives is relevant to the overall conformations and the properties of peptides, both free and protected, as the peptide features are controlled by the energetically favorable or "allowed" conformations of the amino acid residues.[1—5] A recent survey of cysteine-containing molecules in the Cambridge Structural Database[6] revealed that among the cysteine-SH group protections, commonly used in peptide synthesis,[7,8] only the *S*-benzyl (SBzl) present in some derivatives and peptides was investigated.[9] The cysteine residue bearing the *S*-trityl group, which is another common blockade of the SH function in peptide synthesis, applied for over 40 years,[7,8,10,11] was not studied so far. Herein we report the crystal structure of *tert*-butyl *N*-*tert*-butoxycarbonyl-*S*-trityl-L-cysteinate,[12] Boc–Cys(Trt)–O*t*Bu (Fig. 1), in which the *tert*-butoxycarbonyl (Boc) and *tert*-butyl (O*t*Bu) are present in addition to the trityl group. This molecule is the first *S*-tritylcysteine derivative studied by X-ray crystallography. The legitimate structural conclusion reached by the X-ray method was examined by the FTIR study of the molecule in solution and by the theoretical calculations in the gas phase.

Experimental

Boc–Cys(Trt)–O*t*Bu was obtained from Cys(Trt) by *O*-*tert*-butylation followed by *N*-*tert*-butoxycarbonylation, purified by silica gel column chromatography and finally crystallized from *n*-hexane (mp 80—82 °C).[12]

Crystal data for $C_{31}H_{37}NO_4S$ (f_w=519.68): crystal system orthorhombic, space group $P2_12_12_1$, a=8.962 (1), b=14.744 (3), c=22.654 (4) Å, V=2993.2 (9) Å^3, Z=4, d_c=1.153 g cm^{-3}, μ (MoK_α)=0.142 mm^{-1}, F(000)=1112. Using a Siemens P3 diffractometer with MoK_α radiation (λ=0.71073 Å) and a crystal of dimensions 0.53×0.38×0.35 mm, 3882 independent reflections were collected at 293 K. Reflections were measured in the θ range 2.27 to 27.55° and the index ranges $0\leq h\leq 11$, $0\leq k\leq 19$, $0\leq l\leq 29$. The position of the S-atom was found from the Patterson synthesis, the rest of the non-H atoms was located on a Fourier map.[13] Primary positions of H-atoms were found from the difference map, and next geometrical constraints, *i.e.*, riding model, were applied. After the full-matrix least-squares refinement of 334 parameters on F^2, the final discrepancy factors were: $R_1=\Sigma||F_O|-|F_C||/\Sigma|F_O|=0.060$, $wR_2=\{\Sigma[w(F_O^2-F_C^2)^2]/\Sigma w(F_O^2)^2]\}^{1/2}=0.118$ [for $F_O^2>2\sigma(F_O^2)$ and with $w=1/[\sigma^2F_O^2+(0.0553P)^2+0.7151P]$; $P=(F_O^2+2F_C^2)/3$], GOOF=1.024, $\Delta\rho=\pm0.35$ e Å^{-3}. Final positional and thermal parameters for non-H atoms are given in Table 1.[14]

The FTIR spectra were recorded at 20 °C on a Philips Analytical PU9800 spectrometer, at 2 cm^{-1} nominal resolution, using a liquid cell (KBr, 0.1 mm) and KBr pellet. The analytical grade *n*-hexane was dried further over P_2O_5, distilled and stored over freshly prepared molecular sieves. The spectra were analyzed with GRAMS/386 program[15] and the accurate positions of the individual component bands were intercepted by a curve-fitting procedure with a mixed (Gauss+Lorenz) profile.

The calculations were carried out with the GAUSSIAN 98 program package[16] on the Cray J916 at the Poznań Supercomputing and Networking Centre, Poland. The results were produced with the DFT method[17] using the B3LYP hybrid functional[18] and the 6-31G** basis set.

Results and Discussion

Molecular Structure Atom numbering of Boc–Cys(Trt)–O*t*Bu is presented in Fig. 2. Selected bond lengths and angles as well as torsion angles are collected in Table 2. In most

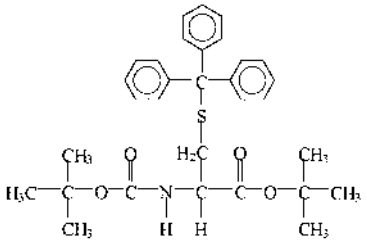

Fig. 1. *tert*-Butyl N^{α}-*tert*-Butoxycarbonyl-L-(*S*-trityl)cysteinate

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Table 1. Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2 \times 10^3$) for Boc–Cys(Trt)–O*t*Bu. U_{eq} is Defined as One Third of the Trace of the Orthogonalized U_{ij} Tensor

Atom	*x*	*y*	*z*	U_{eq}
S (1)	2224 (2)	−203 (1)	1464 (1)	45 (1)
C (2)	3306 (6)	−1110 (3)	1136 (2)	46 (1)
C (1)	3443 (5)	−1870 (3)	1600 (2)	45 (1)
C (3)	4246 (6)	−1513 (3)	2143 (2)	46 (1)
O (2)	3694 (4)	−1449 (3)	2619 (2)	64 (1)
O (1)	5631 (4)	−1278 (2)	1993 (2)	51 (1)
C (4)	6635 (6)	−785 (4)	2404 (3)	59 (2)
C (41)	6953 (7)	−1345 (4)	2943 (3)	74 (2)
C (42)	8028 (7)	−668 (5)	2032 (3)	93 (2)
C (43)	5944 (8)	117 (4)	2553 (3)	81 (2)
N (1)	2045 (5)	−2251 (3)	1777 (2)	50 (1)
C (5)	1308 (6)	−2822 (4)	1417 (3)	57 (1)
O (4)	1804 (5)	−3146 (3)	976 (2)	93 (2)
O (3)	−60 (4)	−2969 (3)	1641 (2)	67 (1)
C (6)	−1125 (7)	−3587 (4)	1347 (3)	62 (2)
C (61)	−1476 (9)	−3238 (5)	748 (3)	103 (3)
C (62)	−2472 (7)	−3532 (5)	1741 (4)	108 (3)
C (63)	−490 (9)	−4530 (4)	1335 (3)	100 (3)
C (7)	2099 (5)	646 (3)	858 (2)	37 (1)
C (8)	3707 (5)	930 (3)	737 (2)	40 (1)
C (81)	4386 (6)	1590 (4)	1078 (3)	58 (2)
C (82)	5869 (7)	1790 (5)	1008 (4)	80 (2)
C (83)	6729 (7)	1350 (5)	615 (3)	80 (2)
C (84)	6098 (6)	691 (5)	269 (3)	69 (2)
C (85)	4582 (5)	484 (4)	334 (2)	51 (1)
C (9)	1146 (5)	1427 (4)	1107 (2)	38 (1)
C (91)	1100 (6)	2252 (3)	803 (2)	52 (1)
C (92)	188 (7)	2949 (4)	998 (3)	62 (2)
C (93)	−674 (6)	2862 (4)	1487 (3)	56 (1)
C (94)	−652 (7)	2066 (4)	1780 (3)	60 (2)
C (95)	261 (6)	1356 (3)	1596 (2)	51 (1)
C (10)	1270 (5)	269 (3)	317 (2)	39 (1)
C (101)	1408 (6)	698 (4)	−226 (2)	50 (1)
C (102)	580 (7)	440 (4)	−707 (2)	67 (2)
C (103)	−410 (7)	−269 (5)	−659 (3)	69 (2)
C (104)	−563 (6)	−699 (4)	−137 (3)	61 (2)
C (105)	250 (6)	−438 (3)	357 (2)	50 (1)

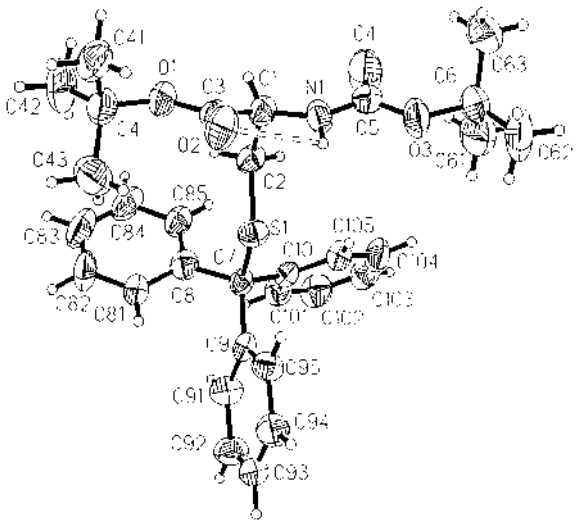

Fig. 2. Molecular Structure of Boc–Cys(Trt)–O*t*Bu, Drawn with 50% Thermal Ellipsoids

The intramolecular hydrogen bond is also illustrated.

Table 2. Selected Bond Lengths (Å) and Angles (°), Experimental (Exp.) from the X-ray Crystal Structure and Calculated (Cal.) from the DFT/B3LYP/6-31G** Method

Bond lengths	Exp.	Cal.		Exp.	Cal.
S(1)–C(2)	1.811 (5)	1.839	N(1)–C(5)	1.346 (6)	1.360
S(1)–C(7)	1.859 (4)	1.895	C(5)–O(4)	1.194 (7)	1.225
C(2)–C(1)	1.541 (6)	1.544	C(5)–O(3)	1.344 (7)	1.355
C(1)–N(1)	1.431 (6)	1.446	O(3)–C(6)	1.478 (6)	1.470
C(1)–C(3)	1.520 (7)	1.534	C(7)–C(8)	1.526 (6)	1.539
C(3)–O(2)	1.189 (6)	1.216	C(7)–C(10)	1.538 (6)	1.548
C(3)–O(1)	1.333 (6)	1.334	C(7)–C(9)	1.540 (7)	1.548
O(1)–C(4)	1.485 (6)	1.484			
Valence angles					
C(2)–S(1)–C(7)	103.1 (2)	102.8	O(4)–C(5)–O(3)	126.2 (6)	126.5
C(1)–C(2)–S(1)	107.5 (3)	110.7	O(4)–C(5)–N(1)	125.1 (6)	123.9
N(1)–C(1)–C(3)	108.8 (4)	107.3	O(3)–C(5)–N(1)	108.7 (5)	109.7
N(1)–C(1)–C(2)	114.0 (4)	114.5	C(5)–O(3)–C(6)	121.3 (5)	121.0
O(2)–C(3)–O(1)	126.7 (5)	126.7	C(8)–C(7)–S(1)	105.1 (3)	106.6
O(1)–C(3)–C(1)	108.9 (5)	110.1	C(10)–C(7)–S(1)	112.0 (3)	112.9
C(3)–O(1)–C(4)	122.1 (4)	122.1	C(9)–C(7)–S(1)	105.5 (3)	104.2
C(5)–N(1)–C(1)	120.3 (5)	122.0			
Torsion angles					
C7–S1–C2–C1	−178.5 (3)	180.0	C1–C3–O1–C4	171.3 (4)	177.1
S1–C2–C1–N1	61.4 (5)	58.4	N1–C1–C3–O1	171.1 (4)	174.4
S1–C2–C1–C3	−60.9 (5)	−64.4	C3–C1–N1–C5	−162.0 (4)	−164.4
C2–S1–C7–C8	−62.3 (4)	−50.7	C1–N1–C5–O3	−170.5 (4)	175.4
C2–S1–C7–C9	178.4 (3)	−171.1	N1–C5–O3–C6	−178.7 (4)	178.9
C2–S1–C7–C10	62.3 (4)	−73.7			

cases, bond lengths observed both for amino acid residue itself and hydrophobic protecting groups are of expected values.

The mean S–CH_2Ph bond length found in the Cys(SBzl) fragments[9] is 1.824 Å, while in the present structure the relevant S1–C7(Trt) distance is 1.859(4) Å. The analysis of the geometry for 11, in total, *S*-trityl fragments occurring in a few organic compounds[19] indicated the S–C(quaternary) bond being in the range 1.866—1.952 Å. Thus, the S1–C7 bond is a slightly shorter one, compared to that in other *S*-trityl fragments, however, it is significantly longer than the S–CH_2Ph bond in the Cys(SBzl) moiety. It seems to explain the much easier detachment of the *S*-trityl group as related to the *S*-benzyl group during the peptide deprotection.[7] At the same time no influence of the bulky *S*-trityl group on the S–C(Cys) distance is observed; the S1–C2 bond of 1.811 (5) Å has a similar length to that in the native L-cysteine molecules (1.798—1.819 Å).[20,21]

The Boc moiety of Boc–Cys(Trt)–O*t*Bu has average bond lengths (Table 2) and the common *trans* conformation in agreement with the literature[2,4] and our CSD search (164 Boc derivatives, of which 158 is *trans*, including four, also *trans*, Boc–Cys fragment[22]). The O*t*Bu moiety of Boc–Cys(Trt)–O*t*Bu has a rigid geometry (the analysis of 87 *tert*-butyl ester fragments, none of which was Cys–O*t*Bu).

The main chain of the molecule C4–O1–C3–C1–N1–C5–O3–C6 adopts extended, nearly all-*trans* C_5 conformation (Table 2) with the torsion angle ϕ −162.0 (4)° and Ψ 171.1 (4)° and with a weak intramolecular N(1)–H···O(2)=C(3) hydrogen bond (Fig. 2). Moreover, the O*t*Bu methyl groups assume specific orientation, pointing to one of the phenyl rings of Trt (Fig. 3). Although the intramolecular multiple (C)H···C contacts of about 3.3 Å are longer than those (up to 3.2 Å) described by Nishio *et al.*,[23] they could prevent free rotation of the bulky trityl and *tert*-butyl substituents. It is worth noting that the recent detailed calculations of intermol-

ecular interaction potentials between the methane and benzene molecule show substantial attraction still existing, even if the intermolecular distance C···C is larger than 4.0 Å.[24)]

Crystal Structure A detailed analysis of the crystal structure of amino acid Boc-derivatives, mentioned above, showed that the urethane NH group in about 90% of the cases is involved in an intermolecular N–H···O=C hydrogen bond. However, in the present structure, there is no intermolecular N–H···O=C bond, because, due to bulky protecting groups, the NH (urethane) group forms the intramolecular hydrogen bond. It is known[8)] that the formation of conventional[25a)] intermolecular hydrogen bonds causes the undesired aggregation of peptide chains during the synthesis of some peptide sequences. The –Cys(Bzl)– residue was measured to have moderate potential for this aggregation.[26)] The lack of strong intermolecular hydrogen bonds in the packing of Boc–Cys(Trt)–O*t*Bu molecules suggests a smaller potential in question for the –Cys(Trt)– residue than the potential for the –Cys(Bzl)– residue. Since the terminally blocked structure of the Boc–Cys(Trt)–O*t*Bu molecule reduces the number of conventional hydrogen-bond donors and/or acceptors, crystal packing (Fig. 4) is mainly dependent on weak hydrogen bonds and hydrophobic contacts. These are illustrated in Fig. 5.

The column of molecules transformed by translation along the *x* axis is stabilized by multiple phenyl···phenyl contacts; ring C(8*n*) is locked between C(9*n*) and C(10*n*) phenyl rings, the C(83)–H(83) and C(84)–H(84) bonds are perpendicular to the C(9*n*)*A* plane. There are two kinds of interactions between molecular columns; both involve phenyl rings.

1. Phenyl H-atoms form C–H···O hydrogen bonds[25)] with two carbonyl oxygen atoms as acceptors (C···O *ca*. 3.5 Å, H···O *ca*. 2.8 Å and ∠C–H···O *ca*. 130°).

2. The phenyl π-system is an acceptor of methyl H-atoms in weak contacts of the CH/π type with the L-shaped geometry.[27)] The strongest of aliphatic/aromatic interactions involve the *tert*-butyl C(41) and C(42) methyl groups and the trityl C(9*n*) phenyl ring (C···C *ca*. 3.7 Å).

An interesting case for supramolecular chemistry is co-op-

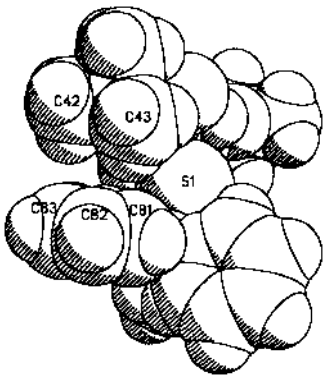

Fig. 3. Relative Orientation of the O*t*Bu Methyl Groups and the C(8*n*) Phenyl Ring in the Boc–Cys(Trt)–O*t*Bu Molecule

Atoms are represented as spheres of respective van der Waals radii.

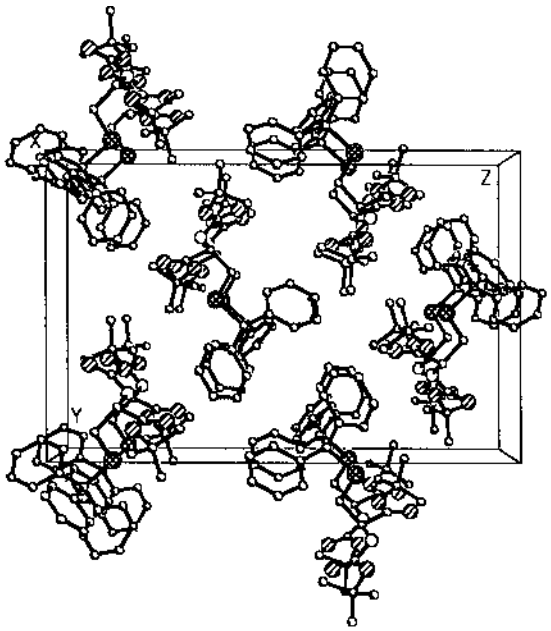

Fig. 4. View of the Crystal Packing along the *x* Axis

The hydrogen atoms are not shown.

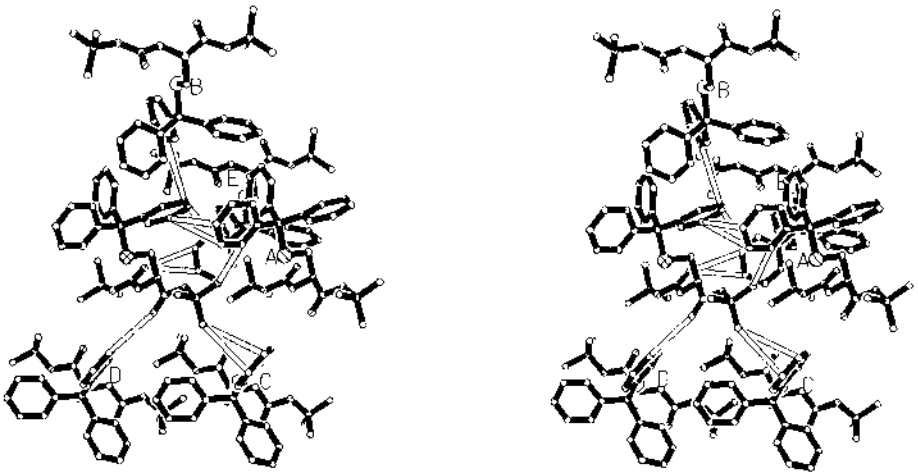

Fig. 5. Stereoscopic Illustration of Intermolecular C–H···O and CH/π Contacts (Marked as Open Lines Linking Donor and Acceptor)

Symmetry codes for molecules are: *none* (*x*, *y*, *z*); *A* (*x*+1, *y*, *z*); *B* (*x*+0.5, 0.5−*y*, −*z*); *C* (1−*x*, *y*−0.5, 0.5−*z*); *D* (−*x*, *y*−0.5, 0.5−*z*); *E* (*x*+0.5, −0.5−*y*, −*z*). Respective distances are: C(93) *D*···O(2) 3.531 (7), C(103) *E*···O(4) 3.494 (8), C(104) *E*···O(4) 3.475 (7) Å for Ph···O; C(41)···C(92) *C* 3.662 (8), C(41)···C(93) *C* 3.762 (8), C(42)···C(95) *A* 3.726 (8) Å for Me···Ph, and C(82)···C(93) *A* 3.643(8), C(82)···C(94) *A* 3.597 (8), C(83)···C(94) *A* 3.686 (8), C(92) *B*···C(84) 3.594 (8) Å for Ph···Ph contacts.

erative interactions to one phenyl ring; the phenyl C(9*n*) atoms accumulate all types of the weak interactions observed in this crystal, *i.e.*, to C=O, phenyl and methyl groups. Those interactions are accompanied by Csp^3/Csp^2 methyl$\cdots$ phenyl contacts with the methyl C–H bond nearly coplanar to the phenyl plane (Fig. 6), which gives a static intermolecular "gearing" structure.[28] The intermolecular C$\cdots$C distances are about 3.8 Å. Such an intermolecular arrangement was also found in aliphatic-aromatic hydrocarbons, *e.g.*, *cis*-4,5-diphenylhex-4-en-2-yne,[29] (*Z*)-2,3-diphenyl-2-butene,[30] *cis*-9,10-diethyl-9,10-dihydroanthracene,[31] and 1,1-diphenyl-2,2-di-(*tert*-butyl)ethene.[32]

Although none of the C$\cdots$O or C$\cdots$C distances fall in the range described as "short",[23,33] the attractive interactions between molecules are strong enough to generate nearly isotropic thermal vibrations of terminal atoms of the Boc–Cys(Trt)–O*t*Bu molecule (Fig. 2). The intra- and intermolecular weak bonding stabilizes the conformation of our molecule and prevents the folding of its hydrophilic part.

Solution and Gas Phase Conformation The Boc–Cys(Trt)–O*t*Bu molecule in the solid state adopts the fully extended C_5 structure of the torsion angles, slightly differing from 180°, and with a weak intramolecular hydrogen bond N(1)–H$\cdots$O(2)=C(3). It is intriguing, as it is well known that such a conformation is not readily accessible in condensed phases to the *N*- and *C*-blocked α-amino acid derivatives due to the weakness of the hydrogen-bonding of this type.[34] Indeed, in our case, FTIR reveals (Fig. 7) that the sample compound in *n*-hexane solution is also largely structureless [$\nu_s(N–H)_{free}$ 3442 cm^{-1}, $\nu_s(C=O_{ester\ free})$ 1741 cm^{-1}, $\nu_s(C=O_{ureth.\ free})$ 1721 cm^{-1}] and only a small fraction exists in the C_5 extended form with a weak hydrogen bond [$\nu_s(N–H)_{bonded}$ 3432 cm^{-1}, $\nu_s(C=O_{ester\ bonded})$ 1731 cm^{-1}, $\nu_s(C=O_{ureth.\ free})$ 1721 cm^{-1}].[35] As seen, even the environment of such an apolar solvent as *n*-hexane disrupts the intramolecular hydrogen bond N(1)–H$\cdots$O(2)=C(3) in a significant population of the molecules. The optimum crystal structure is the result of the competition among many possible so-called packing forces. Hence, we questioned what controls this weak intramolecular hydrogen bond in the Boc–Cys(Trt)–O*t*Bu molecule in its crystal environment. Maybe, the optimum is reached by the adopting of the extended structure by non-relaxed, strained molecules. To verify this hypothesis, we performed the geometry optimization of the molecule *in vacuo* starting with its crystal conformation. The DFT method (which considers electron correlation) with the B3LYP hybrid functional[18] and the 6-31G** basis set was used.

The local minimum has been found and checked by the analysis of harmonic vibrational frequencies. Excluding translational and rotational motions, only positive eigenvalues of the Hessian matrix were obtained, proving that the calculated conformer geometry is a minimum. This gas phase equilibrium geometry has been juxtaposed in Table 2 with the appropriate crystallographic parameters. Given that interatomic equilibrium distances are predicted by the DFT calculations to within 0.02 Å, and bond and torsional angles are found within a few degrees of their experimental values,[36] the gas and the solid state conformation of the main chain of the molecule turned out exactly the same. The extended, in crystal, conformation of the main chain of the Boc–Cys(Trt)–O*t*Bu with the intramolecular hydrogen bond is, therefore, not dictated exclusively by packing. However, small discrepancy between the gas and crystal conformers exists in the side chain arrangement. It concerns all three torsional angles C2–S1–C7–Ph, *i.e.*, the disposition of trityl phenyl rings.

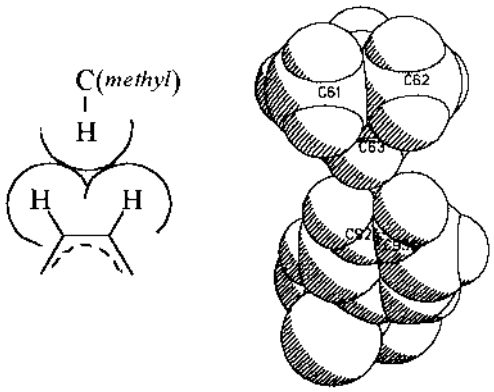

Fig. 6. Intermolecular "Gearing" Phenyl$\cdots$Methyl Interaction

Symmetry codes for molecules are: *none* (*x*, *y*, *z*); *F* (*x*, $-y$, *z*). Respective distances are: C(63)$\cdots$C(92) *F* 3.843 (7), C(63)$\cdots$C(93) *F* 3.864 (8) Å.

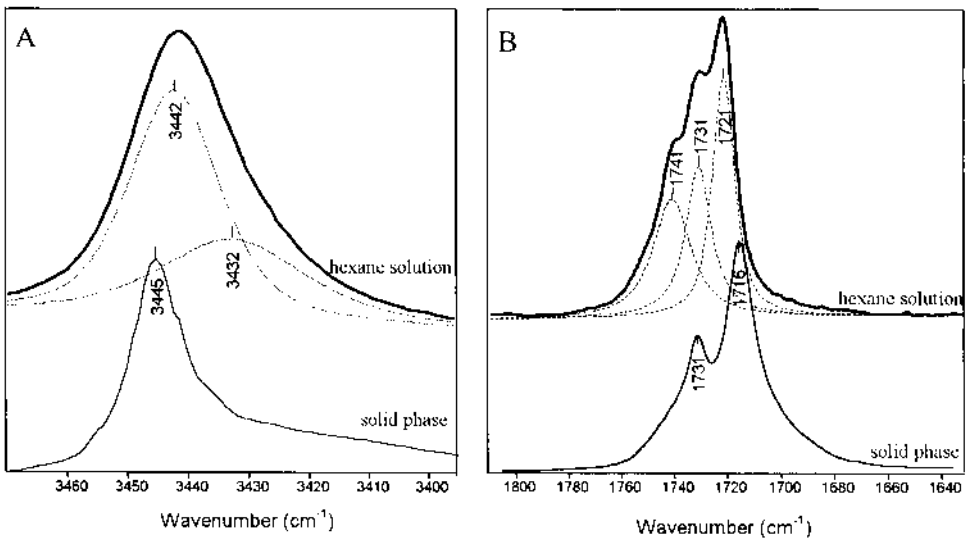

Fig. 7. The FTIR Spectra of Boc–Cys(Trt)–O*t*Bu. (A) ν_s(N–H) Region (Absorption Scale Extended Three Times); (B) ν_s(C=O) Region

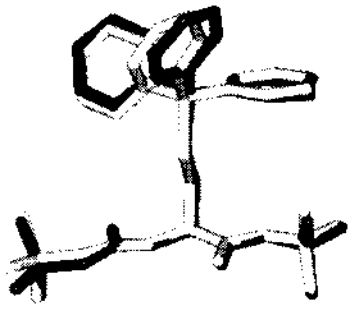

Fig. 8. The Superposition of the Calculated Conformer (black) on the X-ray Conformer (grey) of Boc–Cys(Trt)–OtBu

Each calculated angle differs from its counterpart in crystal by the same few degrees. In consequence, the position of the trityl group as a whole in regard to the main chain is somewhat changed (Fig. 8). The slight reorientation of the trityl group is in line with the formation of the network of the subtle hydrogen bonds and interactions in which the phenyl rings and their protons are involved (Figs. 4 and 5). This specific extensive bonding network provides conformational constraints, which permits the molecule retaining in the solid state its extended conformation with the weak intramolecular hydrogen bond. It contrasts with the behavior of the molecule in the hydrophobic hexane environment in which such specific forces cannot occur.

Conclusion

The comparison of the Boc–Cys(Trt)–O*t*Bu conformation in crystal, solution and in the gas phase suggests the involvement of the side chain of *S*-trityl cysteine in stabilizing the conformation of the main amino acid backbone. Merely slight molecular movement from the gas phase structure turns the side chain trityl group position, allowing for the formation of multiple weak intermolecular C–H$\cdots$O=C hydrogen bonds and CH/π interactions. This bonding network stabilizes a conformational minimum of the main chain of the molecule with its inherent weak conventional N(1)–H$\cdots$O(2)=C(3) hydrogen bond and prevents it from folding in another way to establish an alternative, common, conventional pattern of strong hydrogen bonding. The crystal structure of the studied molecule provides a good example of the involvement of functionless side chains of amino acid residues in the stabilization of the peptide main chain conformation. The stabilization is gained through non-conventional weak hydrogen bonds and interactions. It firmly supports the notion of their significance in the structure and function of peptides.[25b,27] These forces have been recently applied to the construction of the peptide structures of an anticipated biological activity and the importance of this concept was pronounced.[37]

Acknowledgement We thank the Polish State Committee for Scientific Research for a grant-in-aid and the Poznań Supercomputing and Networking Centre, Poland for supercomputer time.

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