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Thiazole–Carbonyl Interactions: A Case Study Using Phenylalanine Thiazole Cyclic Tripeptides

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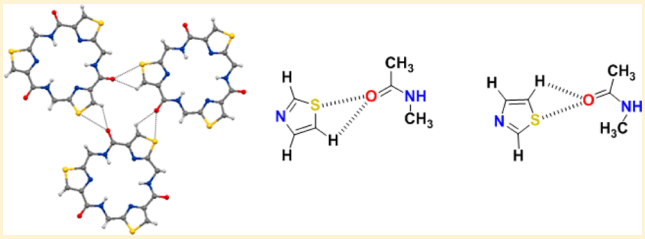
Supporting Information

ABSTRACT: Natural as well as synthetic thiazole/oxazole peptides have shown widespread pharmacological and metal binding properties. Herein, phenylalanine- and tyrosine derived thiazole-containing cyclic tripeptides were synthesized, and the influence of the solvent on the supramolecular assembly in the solid state was investigated. Striking influences of the solvent on the solid state structure were observed. S···O interactions between the sulfur of a thiazole ring and a carbonyl moiety of an amide showing an average distance of 3.1 Å which is much smaller than the sum of the van der Waals radii predominantly mediate the crystal structure. To get deeper insights into this kind of interaction, two model systems consisting of thiazole and acetyl-*N*-methylamide were studied using the MP2/6-311G++(3df,3dp) level of theory. Theoretical calculations revealed that these interactions are associated with an average energy gain of about 16 kJ/mol in comparison with the separated species.



INTRODUCTION

The influence of solvents on the rates of chemical reactions and chemical equilibria has been extensively investigated and has become a central discipline of physical organic chemistry. Studies on solvent–solute interactions reveal that solvophobicity might play a significant role in driving flexible molecules into compact conformations.[1,2] The solvent and noncovalent interactions play a pivotal role in the self-assembly of β-amyloid peptides.[3] The formation of well-ordered supramolecular assemblies of peptides guided by noncovalent interactions has been utilized in the design of peptide nanotubes, nanofibrils, and nanospheres.[4,5] Applications of these peptide nanostructures have been recognized in various fields from antimicrobial agents, regeneration of bone and enamel, cartilage, wound-healing, cardiovascular therapies to molecular electronics.[6] Thus, the selection of an appropriate solvent or solvent mixture is of paramount importance in physical processes such as self-assembly of molecules, recrystallization, chromatographic separations, and catalytic reactions by phase-transfer catalysts, just to name a few. The strengths of solvent–solute interactions depend on a variety of intermolecular forces such as hydrogen bonds, ionic interactions, $\pi\cdots\pi$ interactions, dipole–dipole, lone pair$\cdots\pi$, and other noncovalent interactions.[7,8] Recently, chalcogen–chalcogen[9] interactions have also gained interest across various disciplines. These noncovalent forces are often responsible for molecular recognition events and supramolecular assemblies of compounds containing sulfur, selenium, or tellurium.[10]

A plethora of azole-based cyclic peptides isolated from marine organisms have been reported in the past decade.[11] The broad spectrum of pharmacological properties of these secondary metabolites and the ability to bind metals and to host small molecules have fascinated synthetic as well as natural product chemists.[12,13] A unique and very little explored property of thiazole/oxazole cyclic peptides is the projection of the side chains at one face of the molecule. Nevertheless, Fairlie et al. have shown the effective utilization of side chain orientations in the design of a variety of functional molecules and molecular shapes.[14] However, there is no clear understanding of the molecular behavior of these cyclic peptides containing heterocyclic amino acids in solvents. Such investigations may provide new opportunities to build various molecular architectures, polymorphs, and biomaterials. Herein, we report remarkable supramolecular architectures in the crystal structures of thiazole-containing cyclic tripeptides directed from polar protic, polar aprotic, and nonpolar solvents. In all structures special motifs based on intermolecular chalcogen–chalcogen interactions containing the thiazole moiety play a crucial role.

EXPERIMENTAL SECTION

General Methods. Phenylalanine, tyrosine, DCC, Lawesson's reagent, ethyl bromopyruvate, trifluoroacetic anhydride, trifluoroacetic acid, *N*-hydroxy succinamide, 2,6-lutidine, BOP-Cl, DME, and DIPEA

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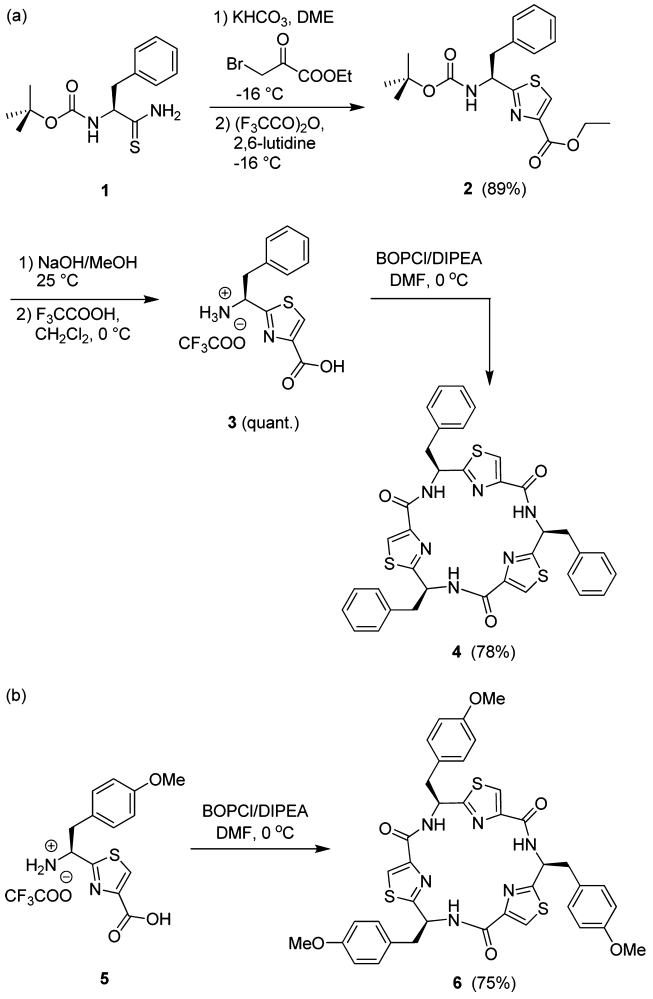
were used as commercially available. THF was dried over sodium and distilled prior to use. Column chromatography was performed on silica gel (100−200 mesh). ^{1}H and ^{13}C NMR were recorded on a 400 MHz instrument (100 MHz for ^{13}C) using the residual solvent signals as an internal reference. The chemical shifts (δ) are reported in ppm and coupling constants (J) are given in Hz. IR spectra were recorded on FT-IR spectrophotometer using KBr pellet. High-resolution mass spectra were obtained from an ESI-TOF MS spectrometer.

(*S*)-Ethyl 2-(1-(*tert*-Butoxycarbonylamino)-2-phenylethyl)-thiazole-4-carboxylate (Ethyl Ester of Boc-Phenylalanine Thiazole 2). 4.38 g (15.6 mmol) of Boc-phenylalanine thioamide **1** in DME (80 mL) was cooled to −16 °C. To this solution 12.50 g (124 mmol) of solid $KHCO_3$ was added under nitrogen atmosphere. The reaction mixture was stirred for another 20 min prior to the addition of 9.73 g (49.9 mmol) of ethyl bromopyruvate. The reaction mixture was stirred at the same temperature for about 30 min and then at room temperature for another 30 min. The reaction mixture was cooled to −16 °C, and then the solution of trifluoroacetic anhydride (8.7 mL, 63 mmol) and 2,6-lutidine (15 mL, 129 mmol) in DME (25 mL) was added in a dropwise manner. The reaction mixture was allowed to reach room temperature and stirred for another 12 h. After the completion of the reaction, volatiles were evaporated under reduced pressure. The reaction mixture was diluted with water and extracted with chloroform (3 × 50 mL). The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. The organic layer was concentrated under reduced pressure and purified by silica gel column chromatography using 20% EtOAc/petroleum ether to afford **2** as a yellowish solid (5.2 g, 89%), mp = 82−84 °C; UV (λ_{max}) = 235 nm; $[\alpha]_D^{20}$ + 9.32 (c = 1, MeOH); IR ν (cm^{-1}) 3352, 2979, 1729, 1693, 1514, 1368, 1251, 1212, 1169, 1093, 1022, 854, 744; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (s, 1H, CH (thiazole)), 7.28−7.22 (dd, 3H, J = 8.3 Hz, 3 × CH (phenyl)), 7.11−7.09 (d, 2H, J = 6.4 Hz, 2 × CH (phenyl)), 5.30 (br., 2H, 1 × NH (Boc), 1 × CH), 4.46−4.40 (q, 2H, J = 6.9 Hz, OCH_2CH_3), 3.36−3.30 (t, 2H, $CHCH_2Ph$), 1.43 (s, 9H, $C(CH_3)_3$) 1.40−1.34 (t, 3H, J = 7.3 Hz, OCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0, 161.3, 154.9, 147.2, 136.1, 129.3, 128.5, 127.1, 80.2, 61.4, 53.8, 41.5, 28.2, 14.3; HRMS (ESI) m/z calcd. for $C_{19}H_{24}N_2NaO_4S$ $[M + Na]^+$ 399.1354, observed 399.1346.

(*S*)-2-(1-Amino-2-(4-methoxyphenyl)ethyl)thiazole-4-carboxylic Acid, 2,2,2-Trifluoroacetate Salt (Phenylalanine Thiazole 3). 2.0 g (5.3 mmol) of Boc-protected phenylalanine thiazole **2** was dissolved in methanol (7 mL). To this stirred solution, NaOH (1 N, 12 mL) was added dropwise. The reaction mixture was stirred for another 1.5 h. After completion of the reaction, the methanol was evaporated and the aqueous layer was acidified with 5% of aqueous hydrochloric acid. The aqueous layer was extracted with EtOAc (3 × 30 mL). The organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The gummy free carboxylic acids was dissolved in dichloromethane (10 mL). To this solution, trifluoroacetic acid (10 mL) was added at 0 °C and stirred for about 1.5 h. After completion of the reaction, the volatiles were removed under reduced pressure and the product (free amino acid) was precipitated using diethyl ether to yield 1.8 g (94%). The free amino acid was directly used in the next step without purification.

Cyclization of Phenylalanine Thiazole 3 to Afford Cyclic Tripeptide 4. 1.80 g (5.0 mmol) of amino acid trifluoroacetate **3** and 3.34 g (7.5 mmol) of BOPCl were dissolved in DMF (140 mL) and cooled to 0 °C. To this solution 5.48 g (42.4 mmol) of DIPEA was added and the reaction mixture was stirred for further 12 h. After completion of the reaction, the solvent was evaporated under reduced pressure and diluted with EtOAc (150 mL). The organic layer was washed with 5% HCl (2 × 50 mL), saturated $NaHCO_3$ solution (3 × 50 mL), brine (50 mL) and dried over anhydrous Na_2SO_4. The organic layer was then concentrated under reduced pressure. The product was purified by silica gel column chromatography using 60% EtOAc/petroleum ether as solvent system to afford 0.926 g (78%) of the pure cyclic tripeptide **4** as a colorless solid, mp = 131−133 °C; UV (λ_{max}) = 230 nm; $[\alpha]_D^{20}$ + 15.63 (c = 1, MeOH); IR ν (cm^{-1}) 3393, 2926, 1668, 1538, 1486, 1277, 1123, 1068, 995, 804, 745, 705; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65−8.63 (d, 3H, J = 8.0 Hz, 3 × NH), 8.02 (s, 3H, C*H*, thiazole), 7.34−7.29, 7.15−7.13 (m, 15H, 15 × CH (Phenyl)), 5.76−5.71 (m, 3H, 3 × $NHCHCH_2$), 3.59−3.54 (dd, 3H, J = 4.6 Hz, $CHCH_2Ph$), 3.13−3.07 (dd, 3H, J = 3.6 Hz, $CHCH_2Ph$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 159.4, 148.5, 135.8, 129.7, 128.6, 127.2, 123.9, 52.7, 44.0, 26.8; HRMS (ESI) m/z calcd. for $C_{36}H_{30}N_6NaO_3S_3$ $[M + Na]^+$ 713.1439; observed 713.1434.

Scheme 1. Synthesis of Thiazole-Containing Cyclic Tripeptides 4 and 6, Respectively



Cyclization of 5 to Afford Cyclic Tripeptide 6. The same protocol as described above was used for the synthesis of the tyrosine-containing cyclic tripeptide **6**. 1.96 g (5.0 mmol) of amino acid trifluoroacetate **5** afforded 1.0 g (75%) of **6** as a white solid; mp = 115−117 °C; UV (λ_{max}) = 228 nm, 251 nm; $[\alpha]_D^{20}$ + 18.42 (c = 1, MeOH); IR ν (cm^{-1}) 3401, 2924, 1665, 1540, 1511, 1383, 1247, 1178, 1107, 1033, 821, 756; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65−8.63 (d, 3H, J = 8.0 Hz, NH, amide), 8.02 (s, 3H, CH(thiazole)), 7.06−7.04 (d, J = 8.8 Hz, 6H, 6 × CH(phenyl)), 6.86−6.83 (d, J = 8.8 Hz, 6H, 6 × CH(phenyl)), 5.70−5.65 (m, 3H, 3 × CH, $NHCHCH_2$), 3.80 (s, 9H, 3 × OCH_3), 3.53−3.48 (dd, 3H, J = 4.4 Hz, $CHCH_2$), 3.06−3.00 (dd, 3H, J = 4.4 Hz, $CHCH_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.4, 159.5, 158.8, 148.6, 130.7, 127.8, 123.9, 113.9, 55.2, 52.9, 43.1; HRMS (ESI) m/z calcd. for $C_{39}H_{36}N_6NaO_6S_3$ $[M + Na]^+$ 803.1756 observed 803.1754.

X-ray Crystallography. Single crystal X-ray data sets were collected on a Bruker APEX DUO CCD diffractometer using Mo K_α radiation (λ = 0.71073 Å) at the desired temperature by using Oxford Instrument Cryojet-HT controller. The collected data were reduced by using program SAINT.[15] Empirical absorption correction was carried out by using the program SADABS.[16] The crystal system was determined by Laue symmetry and space groups were assigned on

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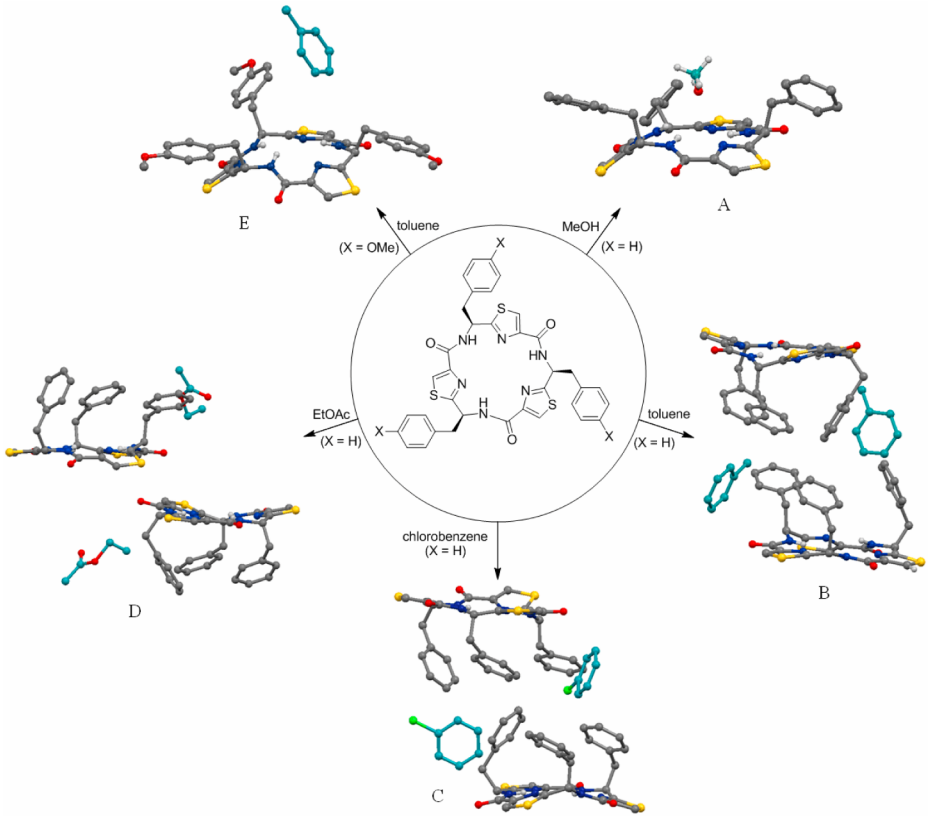

Figure 1. The crystal structures of thiazole cyclic tripeptides **4** and **6**: (A) **4** from methanol, crystal system monoclinic, space group $P2_1$; (B) **4** from toluene, crystal system triclinic, space group $P1$; (C) **4** from chlorobenzene, crystal system triclinic, space group $P1$, (D) **4** from ethyl acetate, crystal system trigonal, space group $P3_2$; (E) **6** from toluene, crystal system orthorhombic, space group $P2_12_12_1$.

the basis of systematic absences by using XPREP. All the structures were obtained by direct methods using SHELXS-97.[17] Hydrogen atoms were fixed geometrically and refined isotropically. ORTEP was used for structure visualization and making the molecular representation. Packing diagrams were generated by using Mercury.

RESULTS AND DISCUSSION

As a part of our ongoing research to study heterocyclic amino acid containing cyclic peptide antibiotics and to understand their molecular architectures and polymorphisms, we synthesized phenylalanine thiazole cyclic peptides. The phenylalanine thiazole ω-amino acid **3** was prepared according to the reported procedures.[14] Key is the reaction of a bromopyruvate with thioamide **1** to assemble the thiazole ring. The macrocyclization of the trifluoroacetate salt of the free amino acid **3** was mediated by BOPCl in the presence of DIPEA (Scheme 1a). The thiazole-containing cyclic tripeptide **4** was isolated in good yield (78%) along with traces of cyclic tetra- and pentapeptides. ^{1}H NMR spectroscopy (in chloroform and in methanol) has unequivocally indicated the C_3-symmetric nature of the molecule. An analogous procedure afforded the tyrosine-derived thiazole cyclic tripeptide **6** starting from amino acid trifluoroacetate salt **5** (Scheme 1b).

Because of our interest in the behavior of the side chains, we tried to get crystals from different solvents. Slow evaporation of a solution of **4** in methanol yielded crystals with a molecular structure shown in Figure 1A. The thiazole-containing cyclic peptide backbone appeared slightly distorted from the planarity (with rms deviation 0.41, see Supporting Information). As anticipated all benzyl groups of the cyclic peptide are projecting at one face of the molecule. Interestingly, the solvent methanol is trapped in the center above the cyclic ring backbone of the tripeptide by forming a weak hydrogen bond (2.693 Å) with the proton of an amide moiety.

All *trans* amide NHs are pointing inside the ring. Inspection of the hydrogen bond parameters reveals that there is no intramolecular hydrogen bond observed between the NH units or with the nitrogen of the thiazole ring.[11f] Examination of the crystal packing reveals that the cyclic peptide adapted a well-organized supramolecular architecture in the crystal (Figure 2A). A network of S···O interactions with a distance of 3.03 Å (the sum of the van der Waals radii of sulfur and oxygen is 3.32 Å) and S···H interactions determines the self-assembly. The most important intermolecular S···O distances are compiled in Table 1. In addition, other interactions such as C−H···π, C−H···O, π···π and S···π interactions support the supramolecular assembly. Details with respect to these distances are provided in Supporting Information.

The serendipity of S···O mediated supramolecular assembly of the tripeptide **4** led us to grow the crystals in toluene, chlorobenzene, and ethyl acetate to further understand the molecular behavior and polymorphisms. The crystals of the cyclic peptide obtained from the solution in toluene revealed a structure as shown in Figure 1B. Surprisingly, the cyclic peptide adapted overall a different type of crystal packing compared to the crystals grown in methanol. The asymmetric unit contains two molecules of the cyclic tripeptide associated with two molecules of toluene. In contrast to the structure in methanol, the tripeptide **4** adapted a closed structure exposing the cyclic backbone for other noncovalent interactions. Two molecules of **4** are connected via toluene through CH···π and C−H···O

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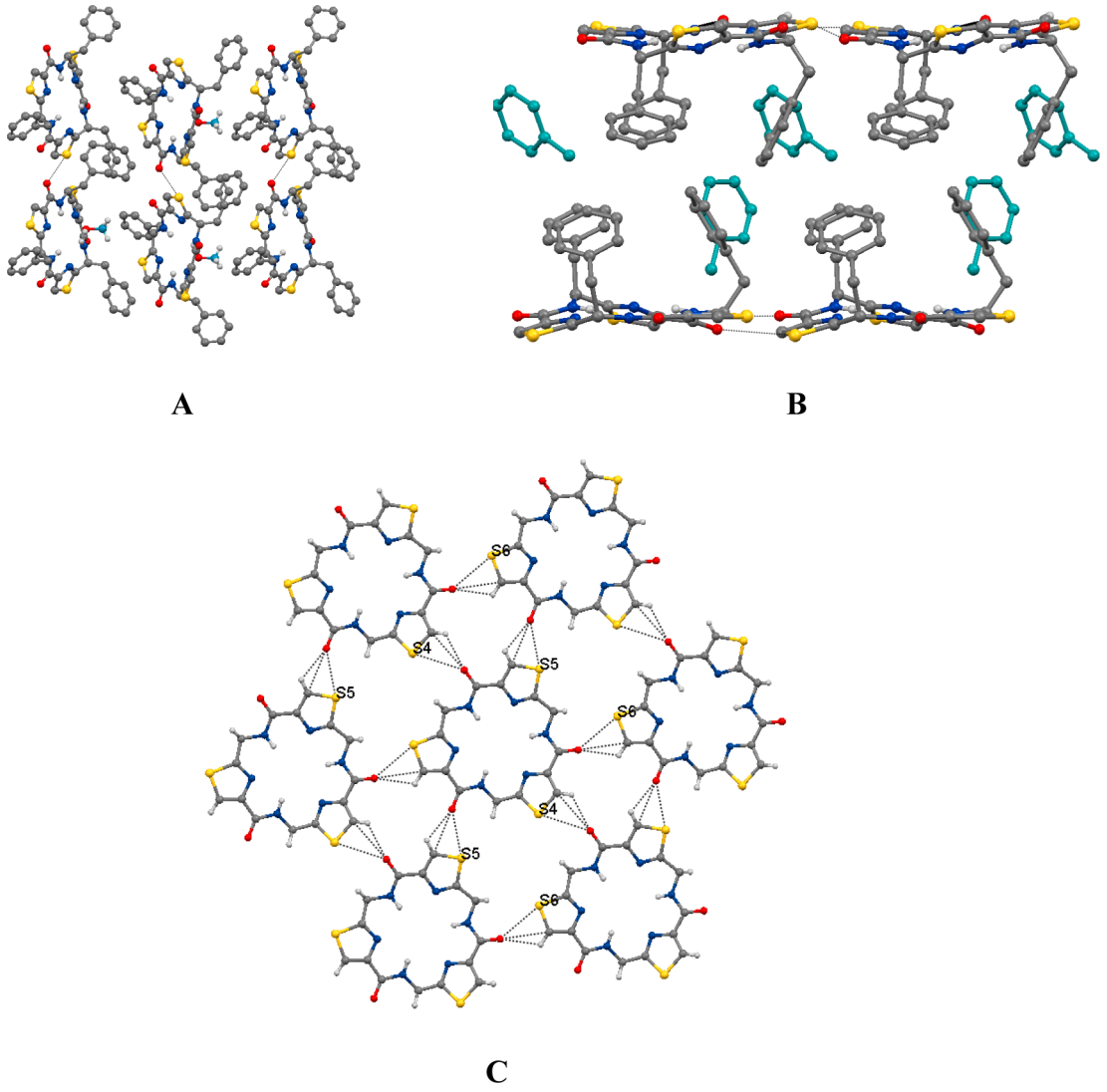

Figure 2. Supramolecular assembly of cyclic tripeptide **4** in methanol (A) and in toluene (B). The solvent molecules are highlighted in light blue. (C) Top view of B showing a network of S···O interactions in the horizontal direction.

Table 1. S···O Interactions Observed in the Crystal Structures of Thiazole Cyclic Tripeptides

crystals from	S···O	*d* [Å]	S···O═C [deg]	crystals from	S···O	*d* [Å]	S···O═C [deg]
4 (MeOH)	S1···O2	3.039	133	**4** (EtOAc)	S5···O8	3.305	140
4 (PhMe)	S1···O2	3.049	146	**4** (PhCl)	S1···O2	3.303	141
	S2···O3	3.219	143		S2···O3	3.249	141
	S3···O1	3.213	143		S3···O1	3.074	146
	S4···O5	3.312	141		S4···O4	3.132	142
	S5···O6	3.055	145		S5···O6	3.064	148
	S6···O4	3.130	143		S6···O5	3.275	141
4 (EtOAc)	S2···O3	3.171	144				
	S3···O1	3.236	141		*O*-methyl tyrosine cyclic tripeptide		
	S4···O7	3.189	143	**6** (toluene)	S2···O6	3.140	149

interactions. The corresponding side view is depicted in Figure 2B. The careful examination of the crystal structure reveals that the supramolecular architecture is stabilized by the six C−H···O and the six S···O interactions in the horizontal direction (Figure 2C). The distances of C−H···O═C interactions lie within the limits of the standard C−H···O distances (2−3 Å),[8] whereas the C−H···O angles were found to be in the range of 108−120°. The carbonyl oxygen is involving in bifurcated C−H···O and S···O interactions. The distances of six different S···O interactions from the top and the bottom plane are in the range of 3.06−3.31 Å (as compiled in Table 1). Similarly, the crystals grown from a solution of chlorobenzene show an isomorphic structure (Figure 1C). Furthermore, the crystal packing is stabilized by six C−H···O and six S···O interactions in the horizontal planes (top and bottom), and the two tripeptides are interconnected by chlorobenzene molecules similar to toluene. The distances and bond angles of S···O interactions are given in Table 1, and the parameters of the other interactions are

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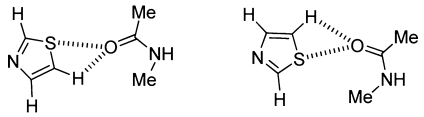
tabulated in Supporting Information. The Cl(1) is involved in a bifurcated hydrogen bonding with C(6)−H and C(50)−H with distances of 2.82 and 2.89 Å and C−H···Cl(1) angles of 152° and 149°, respectively. Interestingly, Cl(2) is involved in a lone pair···π interaction with another molecule of chlorobenzene but not in hydrogen bonding.

Crystals of the peptide obtained from a solution of ethyl acetate revealed the structure shown in Figure 1D. In contrast to the structure obtained from the crystals grown in toluene, the peptide adapted a different packing. The supramolecular assembly of the cyclic peptide is shown in the Supporting Information. Interestingly, the phenyl side chains are directly involved in the C−H···π interaction with phenyl groups of another cyclic peptide in the crystal packing. In contrast to the structures from toluene and chlorobenzene, four S···O interactions (Table 1) along with C−H···O interactions are observed in the horizontal assemblies of both the planes. Instructively, an average C═O···S bond angle of about 143° is observed in all crystal structures.

To further understand the influence of nonpolar solvents in the crystallization of tripeptides with the polar head groups, crystals of the tyrosine-derived cyclic tripeptide **6** were grown from a solution of toluene yielding the molecular solid state structure shown in Figure 1E. Instructively, the peptide adapted a molecular assembly similar to that of **4** obtained from a solution of methanol (Figure 1A). Only one S···O interaction is observed with a distance of 3.14 Å and an S···O═C bond angle of 149°. However, in contrast to the peptide crystals grown in methanol, an interaction of the solvent toluene with the thiazole ring is observed in the tripeptide **6**.

The analysis of the crystal structures from different solvents suggests the striking influence of the solvent in architecting divergent supramolecular assemblies. The cyclic peptides may adopt different molecular conformations based on the polarity of the molecule and the solvent. However, all these divergent supramolecular assemblies are predominantly mediated by S···O interactions. The role of nonbonded intramolecular S···O interactions in organic reactions has been well recognized;[9f,i−m] however, very little is known about intermolecular S···O interactions.

To get deeper insights into the supramolecular assemblies in the solid state and the respective S···O interactions, theoretical calculations were performed. The most striking structural motif is the close contact between a peptidic carbonyl on the one hand side and the sulfur and the hydrogen of the thiazole ring on the other (as depicted in Figure 2C). Therefore, two model systems **7** and **8** consisting of thiazole and acetyl-*N*-methylamide were investigated (Figure 3) by means of the



7 **8**

Figure 3. Simplified predominant motifs **7** and **8** in the solid-state structure of the cyclic thiazoles resulting in an interaction energy of 16.0 kJ/mol (**7**) and 16.6 kJ/mol (**8**), respectively.

MP2/6-311G++(3df,3dp) level of theory.[18,19] Previous studies revealed that such a level of theory provides a very efficient way for estimating coupled cluster interaction energies, whereas the B3LYP method leads to quite good geometries but is incapable of recovering correct interactions energies.[9h,e] For the model systems shown in Figure 3 all the geometrical parameters were optimized with Gaussian03[20] using the counterpoise procedure to obtain a BSSE-corrected supramolecular assembly. Energies were corrected for zero-point and the corresponding geometries were characterized as minima by subsequent frequency calculation. Our investigations revealed several minima, a global one with a skewed arrangement being 20.4 kJ/mol more stable than the separate monomers (see Supporting Information) and the two local ones showing a very similar geometry as observed in the solid-state architecture. The local ones in which the two molecules are almost located in one plane are about 16.0 kJ/mol (**7**) and 16.6 kJ/mol (**8**) more stable than separated thiazole and acetyl-*N*-methylamide. We assume that most of the interaction energy is attributed to dispersion forces; corresponding natural bond orbital (NBO) analyses[21] having been performed on the dimer's optimized geometry did not result in a clear-cut charge transfer from one functionality to another.

■ CONCLUSION

In summary, phenylalanine- and tyrosine-derived thiazole-containing cyclic tripeptides **4** and **6** were synthesized by BOPCl/DIPEA-mediated trimerization of the corresponding amino acids. X-ray investigations performed with crystals obtained from various solvents (methanol, toluene, chlorobenzene, and ethyl acetate) revealed strongly divergent supramolecular assemblies in the solid state. All of them are predominantly mediated by nonbonded intermolecular S···O interactions of a thiazole and a carbonyl unit arranged in a coplanar fashion. Theoretical calculations at the MP2 level of theory using appropriate model systems have shown that a significant energy gain of about 16 kJ/mol is associated with such an arrangement. Thus, interactions with thiazole as the crucial structural element might also play an important role for the biological activity of thiazole-containing cyclic peptide antibiotics and may offer new opportunities for the construction of novel supramolecular assemblies and materials.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

X-ray structure analyses, ^{1}H and ^{13}C NMR spectra, Gaussian Archive Entries, ORTEP diagrams of peptide structures and noncovalent interactions data. Further crystallographic information can be obtained from The Cambridge Crystallographic Data Centre (CCDC) Nos. 807926-807928, 904832 and 904833. This material is available free of charge via Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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