X-Ray structures and *ab initio* study of the conformational properties of novel oxazole and thiazole containing di- and tripeptide mimetics †

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X-Ray crystal structures of Boc-protected derivatives of the novel di- and tripeptide mimetics 2-aminomethyl-1,3-oxazole-4-carboxylic acid, 2-aminomethyl-1,3-thiazole-4-carboxylic acid, 2-(2′-aminomethyl-1′,3′-oxazol-4′-yl)-1,3-thiazole-4-carboxylic acid (gly(OxaThz)), and 2-(2′-aminomethyl-1,3-thiazol-4′-yl)-1,3-thiazole-4-carboxylic acid (gly(ThzThz)) have been determined. Furthermore conformational properties of the bicyclic compounds have been investigated by *ab initio* calculations at the HF and DFT level. According to the calculations for the bicyclic compounds the *anti* conformation is energetically more stable by about 20 kJ mol^{-1} (HF/6-31G(d)) for gly(ThzThz) and gly(OxaThz) while in the case of gly(ThzOxa) the difference is only about 4 kJ mol^{-1}. The rotational barrier is about 28 kJ mol^{-1} for the *anti*→*syn* conversion. Calculations at the DFT level with a 3-21G(d) basis set yielded similar results.

Introduction

The majority of bioactive ligands are peptides or parts of proteins exhibiting a defined topology such as a loop. Therefore drug development based on peptide mimetics that allow the three-dimensional presentation of a variety of functional groups is an often successful approach to obtain ligands of known geometry and topography interacting with receptors. Rigid templates connecting multifunctional sites of a ligand in definable conformations are of particular value to mimic the receptor binding site of a ligand. Small linear and cyclic peptides derived from natural ligands and all kinds of compound libraries which include a large variety of related and functionalized heterocyclic ring systems have been made available.[1]

Recently we reported on the chemical synthesis of naturally occurring heterocyclic amino acids,[2] namely 2-aminomethyloxazole-4-carboxylic acid (gly(Oxa)), 2-aminomethylthiazole-4-carboxylic acid (gly(Thz)), and the novel fused ring systems 2-(2′-aminomethyloxazol-4′-yl)thiazole-4-carboxylic acid (gly(OxaThz)), and 2-(2′-aminomethylthiazol-4′-yl)oxazole-4-carboxylic acid (gly(ThzOxa)). In addition to being natural structural elements of a large number of linear and cyclic bioactive peptides from microorganisms and marine organisms[3] these amino acids can be varied with side chains starting from natural and nonnatural α- or β-amino acids. The knowledge of the structural properties of selected members of these novel building blocks extends the range of rational drug design to di- and tripeptide mimetics which impose total conformational rigidity on the Φ(N–C$_\alpha$) and Ψ(C$_\alpha$–CO) torsional angles. Thus, structural diversity can be created on the basis of the naturally occurring conformationally restricted di- and tripeptidomimetics which can be built in as linkers. Indeed, these heterocyclic ring systems may constitute pharmacophors by themselves as suggested by the bioactivity of natural products such as the gyrase inhibitor microcin B17,[4] antitumor compound bleomycin,[5] other antibiotics, siderophors, and alkaloids. The novel synthons meet all requirements for peptide conformational mimetics: They can be inserted into a peptide chain and enforce a particular conformation, they are compounds with variable amino acids side chains, and they are available as versatile tools and derivatives ready to use in automated synthesis.

The design of peptidomimetics presenting a given topology of functional groups requires information about the conformational properties of the employed building blocks. For the amino acids investigated in this study the arrangement of the heterocyclic rings in the compounds **4** and **5** (Fig. 1) is particularly important. There are two possible planar conformations characterized by the dihedral angle χ between the atoms N(3′)–C(4′)–C(2)–N(3) that should be stabilized by π-conjugation between the heteroaromatic rings. A dihedral angle of $\chi = 0°$ corresponds to a *syn*, one of 180° to an *anti* conformation of the two ring nitrogen atoms with respect to the single bond between the rings. Model building has shown that depending on the dihedral angle the geometry induced by these new building blocks on the peptide is quite different. A dihedral angle of 0° leads to a turn-like motif, whereas a dihedral angle of 180° resembles a more extended structure.

Similar non-fused bicyclic compounds, like biphenyl,[6] 2,2′-biimidazole,[7] 2,2′-bithiophene,[8] and others[9] have been investigated with respect to the rotational conformations. Often the planar conformation is disturbed by steric or electrostatic interactions forcing the molecules into a skewed conformation. In compounds **4** and **5** less steric hindrance should be expected due to the smaller ring size and the lack of hydrogen atoms.

In this paper we report the crystal structures of the amino acids methyl 2-(*tert*-butyloxycarbonylaminomethyl)-1,3-oxa-

† Experimental and calculated structural parameters of **4** to **8** are available as supplementary data from BLDSC (SUPPL. NO. 57696, 3 pp.) or the RSC Library. See Instructions for Authors available *via* the RSC web page (http://www.rsc.org/authors).

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Table 1 Crystallographic data for compounds **1** to **5**

	1	**2**	**3**	**4**	**5**
Temperature/K	213	213	293	213	293
Crystal size/mm^3	0.25 × 0.25 × 0.1	0.3 × 0.2 × 0.05	0.05 × 0.05 × 0.2	0.3 × 0.05 × 0.05	0.5 × 0.4 × 0.4
Molecular formula	$C_{11}H_{15}O_5N_2$	$C_{10}H_{15}N_3O_3S$	$C_{10}H_{15}N_3O_2S_2$	$C_{13}H_{15}N_3O_4S_2{\cdot}C_2H_6OS$	$C_{13}H_{16}N_4O_4S$
Crystal system	Monoclinic	Monoclinic	Monoclinic	Monoclinic	Monoclinic
Space group	$P2_1$	$P2_1/c$	$C2/c$	$P2_1/c$	$P2_1/c$
a/Å	5.0968(8)	23.446(3)	21.506(3)	5.9961(5)	8.832(2)
b/Å	11.0940(5)	7.2220(4)	6.049(2)	23.1990(13)	37.119(4)
c/Å	11.4740(2)	18.670(5)	42.9270(10)	14.149(2)	9.593(2)
β/°	90.455(7)	123.274(7)	103.58(3)	91.140(4)	99.5130(10)
Z	2	8	16	4	8
Reflections collected	1390	4640	8540	4368	6575
Independent reflections	1038	4251 [R(int) = 0.0371]	3570 [R(int) = 0.0600]	3329 [R(int) = 0.0941]	5524 [R(int) = 0.0331]
Reflections observed[a]	1149	3406	2521	2724	4766
θ range for data Collection/°	5 to 69	5.66 to 64.83	5.15 to 64.84	6.25 to 64.89	5.07 to 66.86
Restraints (parameters)	0 (163)	0 (427)	0 (308)	0 (320)	0 (398)
R_1	0.042[b]	0.0505	0.0896	0.0440	0.0531
wR_2		0.1267	0.2288	0.1068	0.1460
Goodness-of-fit on F^2	0.9377[b]	1.101	1.048	1.075	1.059

[a] Criterion for observation: >2$\sigma(i)$. [b] Calculated with the program SDP; refinement against F.

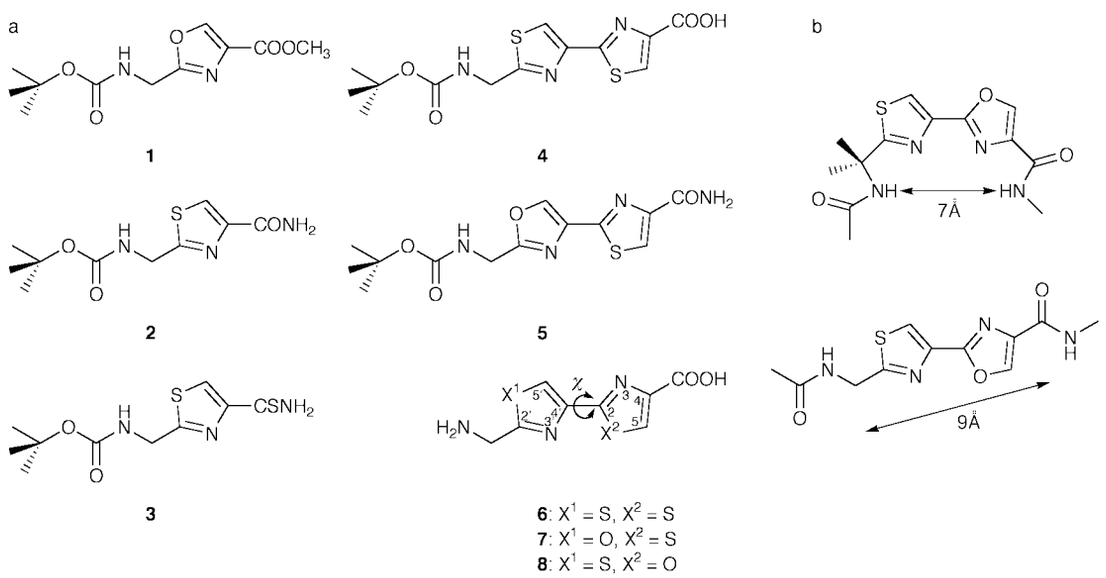

Fig. 1 a, Structures of compounds **1**–**8**. b, Spanning distances of *syn* and *anti* conformations.

zole-4-carboxylate **1**, 2-(*tert*-butyloxycarbonylaminomethyl)-1,3-thiazole-4-carboxamide **2**, 2-(*tert*-butyloxycarbonylaminomethyl)-1,3-thiazole-4-carbothioamide **3**, 2-[2′-(*tert*-butyloxycarbonylaminomethyl)-1′,3′-thiazol-4′-yl]-1,3-thiazole-4-carboxylic acid **4** and 2-[2′-(*tert*-butyloxycarbonylaminomethyl)-1,3-oxazol-4′-yl]-1,3-thiazole-4-carboxamide **5** (Fig. 1). Since the crystal structure can only provide information about the most stable rotamer in the crystal, *ab initio* calculations at the Hartree–Fock and density functional theory level have been employed in order to characterize more closely the conformational properties of the three novel bicyclic tripeptide mimetics gly(ThzThz) **6**, gly(OxaThz) **7**, and gly(ThzOxa) **8** with respect to the orientation of the two heterocyclic rings.

Results and discussion

Crystallographic data for compounds **1** to **5** are given in Table 1. Some selected geometrical parameters of the X-ray structures for compounds **1** to **5** are given in Tables 2 and 3. Fig. 2 shows the plots of the crystal structures of **2** and **5**. All structures exhibit bond lengths and angles in the typical range for the particular type of bond. In both bicyclic compounds **4** and **5** the dihedral angle N3′–C4′–C2–N3 is close to 180° (176.9° for **4**, 167.8°/177.1° for **5**), *i.e.* the molecules adopt an *anti* conformation in the crystal.

The calculated bond lengths and angles agree well with the experimental data for both levels of theory employed.‡ It is well known that bond lengths calculated at the HF level are usually too short while DFT methods tend to overestimate them.[10] In general, bond lengths and angles involving sulfur are poorly predicted by HF and DFT methods, as is also the case in our calculations. At the DFT level the inter-ring bond length is predicted too short by about 0.02 Å compared to the X-ray structure. Going to a larger basis set in the DFT calculations improves the agreement between theory and experiment for the inter-ring bond, but not, however, for the sulfur-containing bonds (results not shown).

The *anti* conformation with a dihedral angle of 180° is a true minimum at both levels of theory as has been confirmed by frequency calculations. Geometry optimization of the *syn* conformation with the HF method, however, leads to a twisted orientation of the heterocyclic rings with a dihedral angle of

‡ Calculated bond lengths and angles are available as supplementary data.

Table 2 Some experimental geometrical parameters of **1** to **3**

	Distances/Å				Angles/°		
	1 X = O	**2** X = S	**3** X = S		**1** X = O	**2** X = S	**3** X = S
X1–C2	1.371(6)	1.730(3)	1.720(9)	N3–C4–C5	111.1(3)	115.4(2)	115.1(6)
X1–C5	1.375(5)	1.704(3)	1.715(7)	C2–X1–C5	105.6(3)	89.22(14)	90.2(4)
H_2C–C2	1.505(5)	1.498(4)	1.506(11)	N3–C4–C	122.2(4)	121.3(2)	125.6(8)
C2–N3	1.297(5)	1.301(3)	1.328(9)	C5–C4–C	126.7(4)	123.2(3)	124.7(8)
C4–C5	1.347(7)	1.353(4)	1.362(12)	X1–C5–C4	106.2(4)	110.4(2)	110.1(7)
N3–C4	1.405(6)	1.386(3)	1.386(11)	C2–N3–C4	103.2(4)	110.0(2)	110.7(7)
C4–C	1.478(5)	1.479(4)	1.473(9)	X1–C2–N3	113.8(3)	114.9(2)	113.9(6)
				X1–C2–CH_2	118.8(3)	121.1(2)	120.4(6)
				N3–C2–CH_2	127.5(5)	123.9(2)	125.6(8)

For numbering of atoms see Fig. 1.

Table 3 Some experimental geometrical parameters of **4** and **5**

	Distances/Å			Angles/°		
	4 X′ = X = S	**5** X′ = O; X = S		**4** X′ = X = S	**5** X′ = O; X = S
X1′–C5′	1.697(3)	1.374(4)	C5′–X1′–C2′	90.0(2)	104.6(2)
X1′–C2′	1.723(3)	1.354(3)	C5–X1–C2	89.28(14)	89.25(13)
X1–C5	1.706(3)	1.697(3)	C2′–N3′–C4′	110.6(2)	105.1(2)
X1–C2	1.735(3)	1.730(3)	C2–N3–C4	109.7(2)	110.0(2)
C2′–N3′	1.301(4)	1.285(3)	N3′–C2′–CH_2	123.6(3)	127.7(3)
N3′–C4′	1.382(4)	1.395(4)	N3′–C2′–X1′	114.4(2)	113.6(2)
C2–N3	1.308(4)	1.307(3)	C5′–C4′–N3′	115.0(3)	108.7(2)
N3–C4	1.383(3)	1.386(3)	C5′–C4′–C2	127.0(3)	131.2(3)
C2′–CH_2	1.493(4)	1.493(4)	C4′–C5′–X1′	110.0(2)	108.1(3)
C4′–C5′	1.366(4)	1.335(4)	N3–C2–C4′	125.8(3)	125.9(2)
C2–C4′	1.460(4)	1.460(4)	N3–C2–X1	115.0(2)	114.7(2)
C4–C5	1.363(4)	1.351(4)	C5–C4–N3	115.9(3)	115.2(2)
C4–CO	1.471(4)	1.486(4)	C4–C5–X1	110.1(2)	110.9(2)

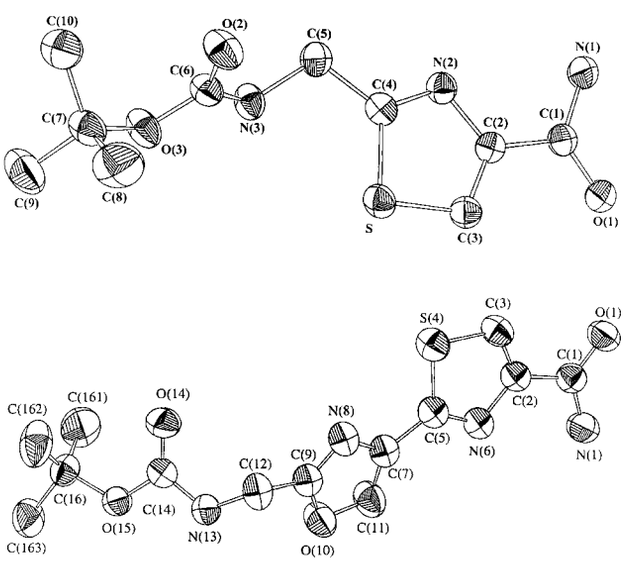

Fig. 2 Plot of one of the structures in the unit cell of compounds **2** (above) and **5** (below).

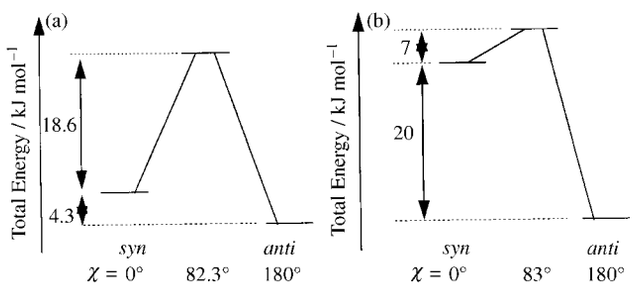

Fig. 3 Sketch of the potential curve for rotation around the inter ring bond in gly(ThzOxa) (a) and gly(OxaThz) (b) calculated at the HF/6-31G(d) level. A similar curve as in (b) results for gly(ThzThz).

18.8 and 19.7° for gly(OxaThz) and gly(ThzThz), respectively. For both molecules the conformation with $\chi = 0°$ is a first-order saddle point with one imaginary frequency, however, for gly(ThzOxa) this conformation is a minimum. The energy difference, though, between the twisted minimum conformation and the planar transition state structure is only 0.21 kJ mol^{-1} for gly(ThzThz) and 0.15 kJ mol^{-1} for gly(OxaThz) and is therefore negligible. In fact, solvent effects probably could remove this barrier in solution. At the DFT level all *syn* conformations have a real minimum at a dihedral angle of 0°.

At the HF level only small changes in bond lengths can be observed in the *syn*-conformer compared to the *anti* conformation. The biggest changes in the range of 0.06 to 0.08 Å occur for the bonds S1–C2 and C2–C4′ in gly(ThzThz) and gly(OxaThz). At the DFT level the changes in bond lengths upon going from the *anti* to the *syn* conformation are slightly larger than in the HF case, especially the bonds S1′–C2′, S1–C2, C4′–C5′, and C2–C4′, which become longer, and C2′–N3′, which becomes shorter.

In Table 4 the calculated energies for compounds **6** to **8** at different levels of theory are listed. In agreement with the crystal structure in all cases the *anti* conformer was more stable than the *syn* conformer. For gly(ThzThz) **6** and gly(OxaThz) **7** the energy difference between the *syn* and *anti* conformation at the HF level is about 20 kJ mol^{-1} while in gly(ThzOxa) the *anti* conformation is energetically more stable by only about 4 kJ mol^{-1}. At the DFT level the energy differences for gly(OxaThz) and gly(ThzThz) are larger by about 6 kJ mol^{-1}, whereas the difference for gly(ThzOxa) is only 2.5 kJ mol^{-1} (Fig. 3).

In order to estimate the energy barrier for rotation around the bond connecting the rings, transition state structures were optimized. The calculated energies are listed in Table 4. In all molecules the dihedral angle χ in the optimized transition state

Table 4 Calculated energies and energy differences for gly(ThzOxa) **8**, gly(OxaThz) **7**, and gly(ThzThz) **6**

	gly(ThzOxa)		gly(OxaThz)		gly(ThzThz)	
	syn	*anti*	*syn*	*anti*	*syn*	*anti*
HF/6-31G*//HF/6-31G*						
ΔE_{tot} [a,b]	−4.356		−20.004		−20.875	
χ [c]	82.3		83.0		84.0	
$\Delta E^{\ddagger}$ [a,b]	18.599	22.955	7.345	27.347	8.134	29.009
B3LYP/3-21G*//B3LYP/3-21G*						
ΔE_{tot} [a,b]	2.450		26.504		27.19	
χ [c]	86.1		83.7		85.1	
$\Delta E^{\ddagger}$ [a,b]	29.68	32.13	14.074	40.578	16.167	43.354

[a] In kJ mol^{-1}. [b] Corrected for the zero point energy with a single scaling factor of 0.9 at the HF and 0.97 at the DFT level. [c] Dihedral angle in the transition state structure, in deg.

structure lies around 84°. Again, gly(OxaThz) and gly(ThzThz) show similar properties. At the HF level the rotational barrier for the *syn–anti* interconversion is about 7 and 8 kJ mol^{-1}, respectively, while in the other direction from the *anti* to the *syn* conformation a barrier of about 28 kJ mol^{-1} has to be overcome. At the DFT level the barriers are considerably higher with approximately 40 kJ mol^{-1} for the *anti*→*syn* and 14 to 16 kJ mol^{-1} for the *syn*→*anti* interconversion. Also for gly(ThzOxa) the barrier is increased from roughly 20 kJ mol^{-1} in the HF calculations to about 30 kJ mol^{-1} at the DFT level.

Conclusion

These calculations show that for the investigated bicyclic amino acids the *anti* conformation is the most stable. The barrier for *syn*→*anti* interconversion is small (of the order of 8 kJ mol^{-1}) and solvent effects could be large enough to further lower this barrier. Therefore only small populations of the *syn* rotamer of gly(ThzThz) and gly(OxaThz) should be found in solution. In the case of gly(ThzOxa), however, the energy difference between the *syn* and *anti* rotamer is much smaller, with similar heights of the barriers for *syn*/*trans* interconversion, and therefore a considerable population of molecules in the *syn* conformation should exist in solution.

The results of this work may open the way for the application of these novel building blocks in the design of peptidomimetics, and also in combinatorial compound libraries[11] for the search of pharmaceutical lead structures. The investigated bicyclic compounds exhibit a substantial difference in conformational behaviour. Assuming a turn like conformation for gly(ThzOxa) in a peptide chain the distance between the *N*-terminal nitrogen and the *C*-terminal nitrogen in the building block is approximately 7 Å. On the other hand, in the extended *anti* conformation gly(ThzThz) and gly(OxaThz) can span a distance of approximately 9 Å in the peptide chain (from N to N, Fig. 1). Work is in progress in order to test the applicability of these results.

Experimental

Heterocyclic di- and tripeptide mimetics

The compounds **1**–**4** have been prepared in multi-step syntheses by solution phase chemistry according to procedures reported previously.[2] All compounds have been recrystallized and characterized by HPLC, ESI-MS, ^{1}H and ^{13}C NMR spectroscopy. Single crystals suitable for X-ray crystallography were obtained as follows: **1** from ether–*n*-hexane**,** **2** from ethanol–ether–*n*-hexane, **3** from ethanol–*n*-hexane, **4** from ethyl acetate–ether, **5** from ethanol–water**.** Boc and Fmoc protected thiazole and oxazole containing amino acids and peptides are available from EMC microcollections, D-72070 Tübingen, Germany. The novel building blocks have been incorporated into small, cyclic or large peptides such as the 43-peptide antibiotic microcin B17, which contains eight of these residues.[12]

Synthesis of 2-(2′-*tert*-butyloxycarbonylaminomethyl-1′,3′-oxazol-4′-yl)-1,3-thiazole-4-carboxamide (5)

Conc. aqueous ammonia (10 ml) was added to Boc-gly-(OxaThz)-COOEt[2] (0.1 g, 0.28 mmol) in ethanol (15 ml) and stirred at room temperature for 12 h. After evaporation *in vacuo* 10% $NaHCO_3$ (20 ml) was added. The crude product was then filtered off, washed with water and recrystallized from ethanol–H_2O. Yield 82 mg (90%); homogeneous in TLC system $CHCl_3$–MeOH–AcOH (95 : 5 : 3) on silicagel plates.

Crystal structure determination

Crystal structures have been determined for the molecules **1** to **5**. X-ray data were collected on an Enraf-Nonius automatic CAD4 diffractometer using Cu-K_α. radiation (λ = 1.54184 Å). Unit cell parameters were obtained from least-squares refinement of the setting angles of 25 reflections, usually in the range of θ = 17 to 22°. Crystallographic data for the molecules are given in Table 1 (CCDC reference number 188/230). The structures were solved using the SHELXS-86 computer program package[13] and refined by a full-matrix least-squares procedure with the SHELXL-93 computer program.[14] The structure of compound **1** was determined with the program SDP.[15]

Computational methods

Ab initio calculations have been carried out using the Gaussian 94 set of programs[16] on different platforms (Cray C94, Convex C3860, and IBM RS/6000). The geometries of the molecules **6**, **7**, and **8** were fully optimized at the restricted Hartree–Fock (RHF) level with the 6-31G(d) basis set[17] and at the density functional theory (DFT) level with the hybrid of Becke's non-local three-parameter exchange and correlated functional[18] with the Lee–Yang–Parr correlation functional[19] (B3LYP) and the 3-21G(d) basis set.[20] Transition states for the rotation around the inter-ring bond were located using the corresponding option for geometry optimization in the Gaussian 94 program package. Frequency calculations were performed on the optimized geometries at the RHF/6-31G(d) and B3LYP/3-21G(d) level of theory with the standard procedures incorporated in the program package. For the calculation of energy differences and barrier heights between different conformers the total energies were corrected for the zero-point vibrational energy scaled by a factor of 0.9 for HF and 0.97 for DFT level of theory. Gaussian output files were analyzed and the structures visualized with the program Molden[21] Ver. 3.2 on a Silicon Graphics workstation.

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