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A Cyclic Side-Chain-Linked Biphenyl Ether Tripeptide: H_3N^+-*cyclo*-[$Phe^{(4-O)}$-Phe-$Phe^{(3-O)}$]-OMe.Cl^-

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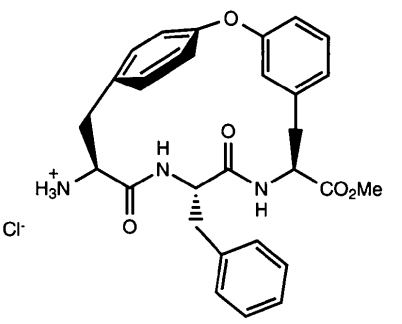
Abstract

The crystal structure of the chloride salt of H_3N^+-*cyclo*-($Phe^{(4-O)}$-Phe-$Phe^{(3-O)}$)-OMe, *cyclo*-phenylalanyl-phenylalanyl-phenylalaninium chloride methyl esther, $C_{28}H_{30}N_3O_3^+.Cl^-$, is described. It is oxidatively linked through a biaryl ether linkage formed from the hydroxyl of 4-hydroxyphenylalanine and the *meta* position of the distal phenylalanine residue. This is the first reported crystal-structure determination of a cyclic 17-membered biphenyl ether tripeptide, a class which includes the natural products K-13 and OF4949 I–IV. An unusual C—H···O hydrogen bond is formed between the methine H atom of the N-terminal Cα and a carbonyl-O atom of a neighboring molecule [C···O = 2.995 (4) Å].

Comment

We are interested in the synthesis and conformation of cyclic biphenyl ether peptides related to natural products K-13 (Yasuzawa, Shirahata & Sano, 1987) and OF4949 I–IV (Sano *et al.*, 1986). During our synthesis of cyclic biphenyl ethers *via* S_NAr macrocyclizations of peptidyl ruthenium π-arene complexes (Janetka & Rich, 1995), we became interested in elucidating their crystal structures. The only other structures available are from NMR (Hobbs & Still, 1989; Yasuzawa, Shirahata & Sano, 1987; Sano *et al.*, 1986). We were unable to crystallize N-protected cyclic biaryl ether tripeptides but were able to crystallize the hydrochloride salt of the free amino cyclic biphenyl ether tripeptide H_3N^+-*cyclo*-[$Phe^{(4-O)}$-Phe-$Phe^{(3-O)}$]-OMe, (I), from ethanol.



(I)

The two rings of the cyclic biaryl ether are in different orientations (Fig. 1). The *para*-substituted ring is rotated out of the plane of the *meta*-substituted ring by 83.3°. As a consequence of this twisting, the *ortho*-H atom [H(C25)] of the *meta*-substituted ring is located near the shielding region of the *para*-substituted ring which is consistent with the upfield shifted resonance in the NMR spectrum for this aromatic proton.

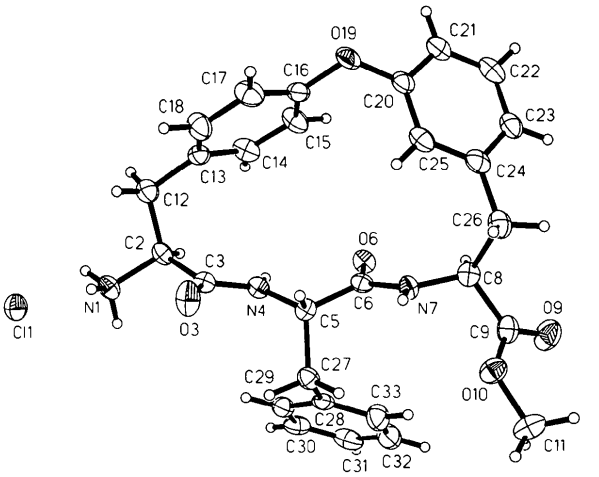


Fig. 1. Plot of the title compound with the atomic numbering scheme. Displacement ellipsoids are plotted at the 50% probability level.

The tripeptide backbone φ and ψ torsion angles (Table 2) are similar to the torsion angles of a β-sheet motif (φ −120°, ψ 120°). Thus, the cyclic 17-membered biphenyl ether tripeptide ring system is a conformational mimic of a β-sheet. As seen in the crystal structures of enzyme-inhibitor complexes, many protease inhibitors bind in an extended β-sheet conformation (Rich, 1990; Swain *et al.*, 1990). This compound can be expected to be a good mimic of protease inhibitors.

Two molecules stack one on top of the other along the *a* axis (Fig. 2) with the peptide of a lower molecule forming one β-sheet hydrogen bond to an upper

neighbor [N7···O6(1+ x, y, z) = 3.192 (4) Å]. However, the second amide proton (HN4) does not form any hydrogen bonds in the lattice. Instead, the carbonyl O atom (O3) forms an unusual C—H···O hydrogen bond (Desiraju, 1991) with the acidic proton on the N-terminal Cα carbon [C2···O3^{i} = 2.995 (4) Å, C2–HC2···O3^{i} = 158.80 (9)°; (i) = x − 1, y, z]. This H atom is affected by the charged amino group of the *R*—C2—$H_3N^+Cl^-$ cluster (Taylor & Kennard, 1982). The chloride ion forms a salt bridge to the terminal amino group of neighboring molecules to form an extensive packing arrangement.

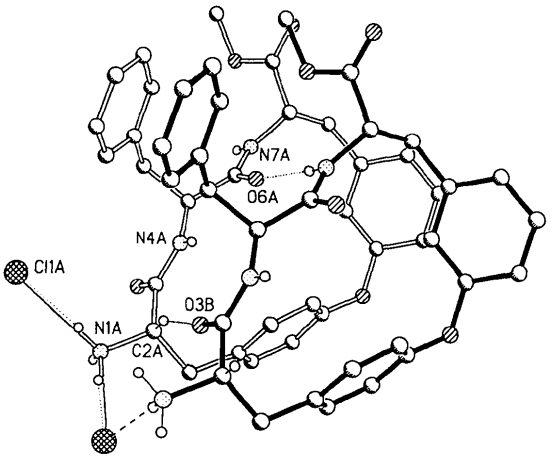


Fig. 2. The β-sheet hydrogen bonding of two molecules in the cell viewed down the short axis.

Experimental

The biaryl ether was synthesized from an S_NAr macrocyclization of Boc–Phe(4-Cl)[RuCpPF$_6$]–Phe–Phe(3-OH)–OMe with sodium 2,6-di-*tert*-butylphenoxide followed by photolytic decomplexation and N-deprotection with 4N HCl/dioxane (Janetka & Rich, 1995). The hydrochloride salt was crystallized from ethanol.

Crystal data

$C_{28}H_{30}N_3O_5^{\ddagger}.Cl^-$
M_r = 524.00
Orthorhombic
$P2_12_12_1$
a = 5.1536 (2) Å
b = 12.4441 (3) Å
c = 41.2592 (11) Å
V = 2646.03 (14) Å^3
Z = 4
D_x = 1.315 Mg m^{-3}
D_m not measured

Mo $K\alpha$ radiation
λ = 0.71073 Å
Cell parameters from 6198 reflections
θ = 2.0–26.0°
μ = 0.187 mm^{-1}
T = 133 (2) K
Needle
0.52 × 0.08 × 0.04 mm
Yellow

Data collection

Siemens *P*4 CCD diffractometer
φ scans
Absorption correction: none
10131 measured reflections
4582 independent reflections

4062 observed reflections [$I > 2\sigma(I)$]
R_{int} = 0.0462
θ_{max} = 26.06°
h = −6 → 3
k = −14 → 11
l = −48 → 50

Refinement

Refinement on F^2
$R(F)$ = 0.0497
$wR(F^2)$ = 0.1033
S = 1.129
4580 reflections
335 parameters
H atoms riding
$w = 1/[\sigma^2(F_o^2) + (0.0216P)^2 + 2.8074P]$
where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.003
$\Delta\rho_{max}$ = 0.247 e Å^{-3}
$\Delta\rho_{min}$ = −0.220 e Å^{-3}

Extinction correction: *SHELXTL* (Sheldrick, 1994)
Extinction coefficient: 0.0035 (5)
Atomic scattering factors from *International Tables for Crystallography* (1992, Vol. C, Tables 4.2.6.8 and 6.1.1.4)
Absolute configuration: Flack (1983)
Flack parameter = 0.11 (9)

Table 1. *Fractional atomic coordinates and equivalent isotropic displacement parameters (Å^2)*

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

	x	y	z	U_{eq}
Cl1	0.2196 (2)	0.40674 (7)	0.98175 (2)	0.0304 (2)
N1	−0.2850 (6)	0.2731 (2)	0.96502 (6)	0.0275 (6)
C2	−0.3479 (6)	0.2325 (3)	0.93214 (8)	0.0252 (8)
C3	−0.1403 (6)	0.1522 (3)	0.92189 (8)	0.0238 (7)
O3	0.0903 (4)	0.1741 (2)	0.92534 (7)	0.0384 (7)
N4	−0.2220 (5)	0.0614 (2)	0.90817 (6)	0.0231 (6)
C5	−0.0395 (7)	−0.0154 (3)	0.89445 (8)	0.0238 (7)
C6	−0.1720 (6)	−0.0768 (3)	0.86709 (7)	0.0230 (7)
O6	−0.4112 (4)	−0.0794 (2)	0.86394 (5)	0.0269 (6)
N7	−0.0047 (6)	−0.1284 (2)	0.84745 (6)	0.0235 (6)
C8	−0.0819 (7)	−0.2061 (3)	0.82281 (8)	0.0274 (8)
C9	0.0213 (7)	−0.3177 (3)	0.83016 (9)	0.0303 (8)
O9	−0.0830 (5)	−0.3983 (2)	0.82122 (7)	0.0462 (7)
O10	0.2443 (5)	−0.3156 (2)	0.84662 (6)	0.0345 (6)
C11	0.3548 (8)	−0.4195 (3)	0.85507 (11)	0.0454 (10)
C12	−0.3585 (8)	0.3297 (3)	0.90898 (8)	0.0319 (9)
C13	−0.3365 (7)	0.2997 (3)	0.87326 (8)	0.0262 (8)
C14	−0.5049 (7)	0.2273 (3)	0.85914 (9)	0.0322 (9)
C15	−0.4710 (7)	0.1943 (3)	0.82713 (8)	0.0340 (9)
C16	−0.2676 (7)	0.2367 (3)	0.80922 (8)	0.0261 (7)
C17	−0.1031 (7)	0.3120 (3)	0.82264 (9)	0.0354 (9)
C18	−0.1401 (8)	0.3421 (3)	0.85460 (9)	0.0362 (9)
O19	−0.2292 (6)	0.2095 (2)	0.77687 (5)	0.0360 (6)
C20	−0.2665 (7)	0.1023 (3)	0.76868 (7)	0.0298 (8)
C21	−0.4448 (8)	0.0780 (3)	0.74445 (8)	0.0335 (9)
C22	−0.4736 (8)	−0.0275 (3)	0.73499 (9)	0.0373 (9)
C23	−0.3262 (7)	−0.1079 (3)	0.74923 (8)	0.0330 (9)
C24	−0.1459 (7)	−0.0846 (3)	0.77320 (8)	0.0304 (8)
C25	−0.1169 (7)	0.0224 (3)	0.78286 (8)	0.0305 (9)
C26	0.0127 (8)	−0.1727 (3)	0.78853 (8)	0.0344 (9)
C27	0.0717 (6)	−0.0935 (3)	0.92045 (8)	0.0267 (7)
C28	−0.1262 (7)	−0.1700 (3)	0.93440 (8)	0.0250 (8)
C29	−0.2911 (7)	−0.1387 (3)	0.95920 (8)	0.0287 (8)
C30	−0.4753 (8)	−0.2088 (3)	0.97158 (9)	0.0346 (9)
C31	−0.4954 (9)	−0.3117 (3)	0.95977 (9)	0.0430 (10)
C32	−0.3275 (9)	−0.3455 (3)	0.93550 (9)	0.0470 (11)
C33	−0.1458 (8)	−0.2747 (3)	0.92280 (9)	0.0390 (10)

Table 2. *Selected geometric parameters (Å, °)*

N1—C2—C3—N4	135.4 (3)	C6—N7—C8—C9	−115.6 (3)
C3—N4—C5—C6	−151.7 (3)	C6—N7—C8—C26	122.6 (3)
N4—C5—C6—N7	163.4 (3)		

Data collection: *SMART* (Siemens, 1994). Cell refinement: *SAINT* (Siemens, 1995). Data reduction: *SAINT*. Program(s) used to solve structure: *SHELXTL* (Sheldrick, 1994). Program(s) used to refine structure: *SHELXTL*. Molecular graphics: *SHELXTL*. Software used to prepare material for publication: *SHELXTL*.

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Lists of structure factors, anisotropic displacement parameters, H-atom coordinates and complete geometry have been deposited with the IUCr (Reference: SX1013). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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meso-(3,5-Di-*tert*-butylphenyl)-2,2′-dipyrromethane

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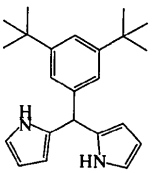
Abstract

In molecules of the title compound, *meso*-(3,5-di-*tert*-butylphenyl)methylenebis(2-pyrrole), $C_{23}H_{30}N_2$, the moieties surrounding the *meso*-C atoms form a tetrahedral geometry. There is no N—H···N hydrogen bonding present in the compound and molecules interact with each other through weak N—H···π interactions.

Comment

One-flask syntheses of *meso*-substituted β-unsubstituted dipyrromethanes have been reported recently (Hammel, Erk, Schuler, Heinze & Müllen, 1992; Lee & Lindsey, 1994). This easy access to *meso*-substituted dipyrromethanes provides a route to the direct synthesis of β-unsubstituted *trans*-substituted porphyrins. The structure of the title compound is equivalent to a $\frac{3}{8}$ segment of the tetraarylporphyrinogen, a cyclic intermediate in Lindsey's method of porphyrin synthesis (Lindsey, Schreiman, Hsu, Kearney & Marguerettaz, 1987). Based on the computational molecular modelling of *meso*-substituted dipyrromethanes, *i.e.* 5-mesityldipyrromethane, it was shown that the extent of the steric hindrance around the *meso*-C atom of the *meso*-substituted dipyrromethane affects the yields in synthesizing *ortho*-disubstituted tetraphenylporphyrin (Lindsey & Wagner, 1989). We present here the crystal structure of *meso*-(3,5-di-*tert*-butylphenyl)-2,2′-dipyrromethane, (I).



(I)

To our knowledge, this is the first structure report on a *meso*-substituted β-unsubstituted dipyrromethane. The crystal structure (Fig. 1) of (I) shows a slightly distorted tetrahedron around the *meso*-C atom, with an average

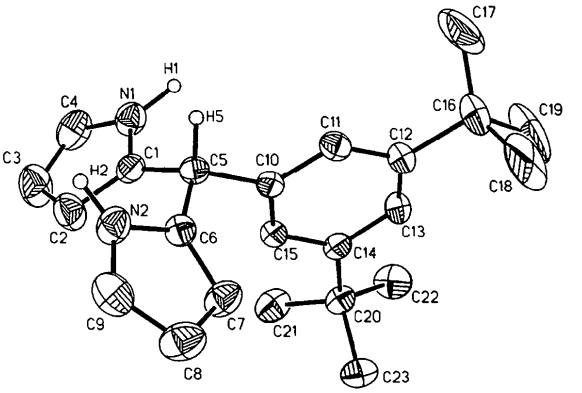


Fig. 1. The atomic labelling scheme for (I). H atoms have been omitted for clarity, except for H1, H2 and H5 on the pyrrole N and *meso*-C atoms, respectively. Displacement ellipsoids are drawn at the 30% probability level.