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Facile synthesis of 2,3,7,8-tetramethyl-2,2′-dipyrrin trifluoroacetate and its X-ray crystal structure

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Abstract 3,4-Dimethyl-1*H*-pyrrole-2-carboxylic acid was converted to 2,3,7,8-tetramethyl-2,2′-dipyrrin by the action of trifluoroacetic acid and ethyl orthoformate. A crystal of the dipyrrin was grown from dichloromethane-*n*-hexane and an X-ray crystallographic structure of its trifluoroacetate salt was determined.

Keywords Pyrrole; NMR; X-Ray.

Introduction

Pyrromethenes (dipyrrins) have been known since early in the last century, due mainly to the extensive synthetic efforts of *Hans Fischer*'s group at the TH-München and summarized in volume II (1st half) [1] of the classic three-volume reference set by *Fischer* and *Orth*. Among the nearly 300 dipyrrins synthesized and described by *Fischer et al.* only one was unsubstituted at carbons 1 and 9: 2,8-diethyl-3,7-dimethyldipyrrin. It was reported and characterized as the hydrobromide salt and was prepared by heating opsopyrrole (3-ethyl-2-methyl-1*H*-pyrrole) with anhydrous formic acid followed by treatment with hydrobromic acid. Subsequent to *Fischer*'s studies, in the last quarter of the 1900s, there was a renewed interest in dipyrroles, and new and varied dipyrrins were synthesized [2].

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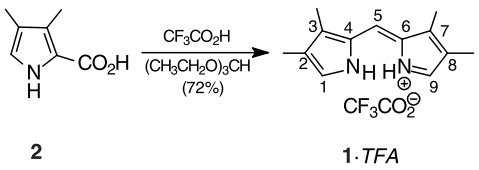
Typically, unsymmetrically-substituted dipyrrins are prepared by acid-catalyzed condensation of a pyrrole aldehyde with an α-H pyrrole. The latter method of course suffices for preparing symmetrical dipyrrins [1–3], which are also now often prepared by heating an α-H pyrrole or an α-carboethoxypyrrole in formic acid-perchloric acid, by treating an α-formylpyrrole with perchloric acid – and isolating the dipyrrins as perchlorate salts [2]. Following this general procedure, **1** · HBr was reported in 1966 [3a] from condensation of 3,4-dimethyl-2-formyl-1*H*-pyrrole with 3,4-dimethyl-1*H*-pyrrole, but no X-ray crystallographic studies have been performed on β-alkyldipyrrins with the free α-positions. We prepared 2,3,7,8-tetramethyl-2,2′-dipyrrin (**1**) (Fig. 1) directly from 3,4-dimethyl-1*H*-pyrrole-2-carboxylic acid (**2**), isolated as its trifluoroacetate salt (**1** · *TFA*), studied its NMR spectra, determined whether it is monomeric in chloroform solution (by vapor phase osmometry, VPO), and carried out an X-ray structure determination of its (amine) salt with trifluoroacetic acid.

Results and discussion

Synthesis aspects

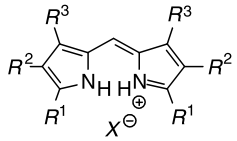
The target dipyrrin (**1**, Scheme 1) was prepared from 3,4-dimethyl-1*H*-pyrrole-2-carboxylic acid (**2**) [4], which was available following saponification of the ethyl ester (**3**) [4–6]. Pyrrole ester **3** was prepared

(A)



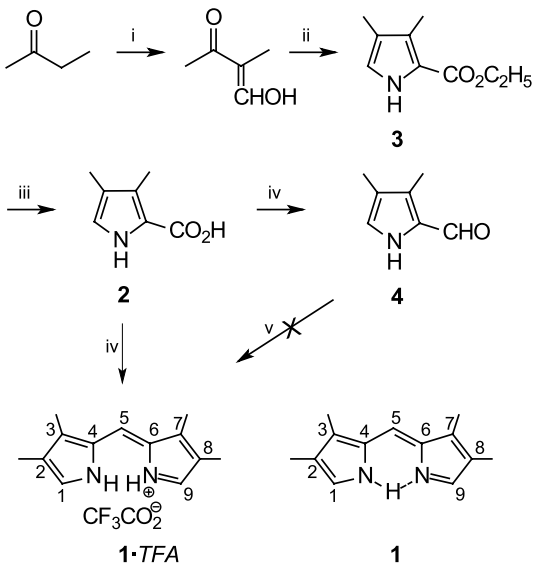
2 1·*TFA*

(B)



	R^1	R^2	R^3	X
5	*Br*	CH_3	CH_2CH_3	Br^-
6	$CO_2CH_2CH_3$	CH_3	CH_3	Br^-
7	CH_3	$(CH_2)_2CO_2CH_2CH_3$	CH_3	Cl^-

Fig. 1 (A) The structure of 2,3,7,8-tetramethyl-2,2′-dipyrrin trifluoroacetate (**1** · *TFA*) and its numbering system. (B) Dipyrrin salts whose X-ray crystal structure had been determined earlier



Reagents and conditions: i, Na/ether, then ethyl formate; ii, diethyl oximinomalonate, Zn, acetic acid; iii, $NaOH/H_2O$; iv, CF_3CO_2H/ethyl orthoformate; v, CF_3CO_2H.

Scheme 1

from simple components, as described in Refs.[4–6]: 2-butanone, ethyl formate, and diethyl oximinomalonate. The *Barton-Zard* reaction [7] of ethyl isocyanoacetate with 2-acetoxy-3-nitro-2-butene, available by acetylation of the condensation product between nitroethane and acetaldehye also leads successfully to **3** [8]. Treatment of **2** with trifluoroacetic acid at 0°C for 15 min, followed by addition of ethyl orthoformate typically gives high yields of the known [3a] 3,4-diethyl-2-formyl-1*H*-pyrrole (**4**) when low temperature is maintained throughout [9]. However, if the trifluoroacetic acid (*TFA*) solution of **2** is allowed to warm to room temperature before adding the ethyl orthoformate, and the reaction is kept at room temperature for one hour, a 72% yield of crystallized **1** is obtained as its trifluoroacetate salt (**1** · *TFA*). Similar treatment of ester **3** did not give **1**; nor did treatment of **4** with trifluoroacetic acid at room temperature. Treatment of **2** with trifluoroacetic acid at room temperature briefly, followed by addition of ethyl orthoformate at 0°C and standing for 7 min at 0°C afforded 2,5-diformyl-3,4-dimethyl-1*H*-pyrrole.

Spectral characterization

No NMR or UV-Vis data had been reported for **1** · HBr [3a]. Dipyrrin **1** · *TFA* exhibited ^1H and ^{13}C NMR spectra expected for a symmetric structure, with each nitrogen bearing a proton intramolecularly hydrogen bonded NH (Scheme 1). Only two different CH_3 signals (2.04, 10.1, 2.27, and 10.5 ppm), were

Table 1 Solvent dependence of the UV-Vis spectral data for **1** · *TFA* (λ_{max} in nm, ε in $dm^3 \cdot mol^{-1} \cdot cm^{-1}$)

λ_{max} (ε) in					
Benzene	Chloroform	Acetonitrile	Methanol	Dimethylsulfoxide	Trifluoroacetic acid
480 (32600)	477 (32500)	469 (29400)	472 (27700)	475 (28600)	469 (29000)

observed, along with one C(1)/C(9) signal (7.62 and 143.1 ppm), and one carbon-13 signal for C(2)/C(8) (144.3 ppm), C(3)/C(7) (126.4 ppm), and C(4)/C(6) (129.0 ppm). In addition, we found signals in the ^{13}C NMR for CF_3CO_2H at 161.5 and 117.5 ppm and in the ^{19}F NMR at −76.3 ppm. Curiously, we found two deshielded signals in the NH region of the ^{1}H NMR: 12.62 and 11.82, one proton each. The data suggest localization of the $CF_3\,CO_2^-$ anion nearer to one NH than to the other. However, this dissymmetry was not evident in the crystal. The UV-Vis spectra (Table 1) are characteristic of dipyrrins [9], with an intense band ($\varepsilon \sim 30000$) near 470–480 nm.

Molecularity in solution by VPO

The molecular weight of **1** · *TFA* in $CHCl_3$ solution at 45°C, determined by vapor pressure osmometry, is 332 ± 10 g/mol. Its formula weight is 314 g/mol. These data indicate that **1** · *TFA* is a monomer in solution over the concentration range studied, 3–9×10^{-3} *M*.

X-Ray crystal structure

Remarkably, despite the very large number of known dipyrrins [1, 2], only one X-ray crystal structure has been reported for a dipyrrin free base, without heteroatoms attached to C(1) or C(9): diethyl 3,7-diethyl-2,8-dimethyldipyrrin-1,9-dicarboxylate [10], although X-ray structure data for per-C-methylated 1,2,3,7,8,9-hexamethyl-2,2′-dipyrrin have apparently been obtained but were unrefined [11]. There are only a few X-ray crystal structures of protonated dipyrrins (Fig. 1). No salts with carboxylic acids have been reported. A suitable crystal of **1** was grown from dichloromethane-*n*-hexane and its X-ray crystal structure was determined (Fig. 2). There are two molecules (A and B) in the unit cell, of nearly identical structure. Both are planar: the N(1)–C(4)–C(5)–C(6) and N(2)–C(6)–C(5)–C(4) torsion angles are −1.8 and 0.8° in A, and −1.2 and 0.5° in B. From the similarities of bond lengths and bond angles in the two pyrrole rings (Fig. 3), which are also similar at most sites to those found in the X-ray structure of 1,9-dibromo-3,7-diethyl-2,8-dimethyl-[2.2]dipyrrin · HBr [10], it may be deduced that the protonated pigment has core skeletal structural symmetry.

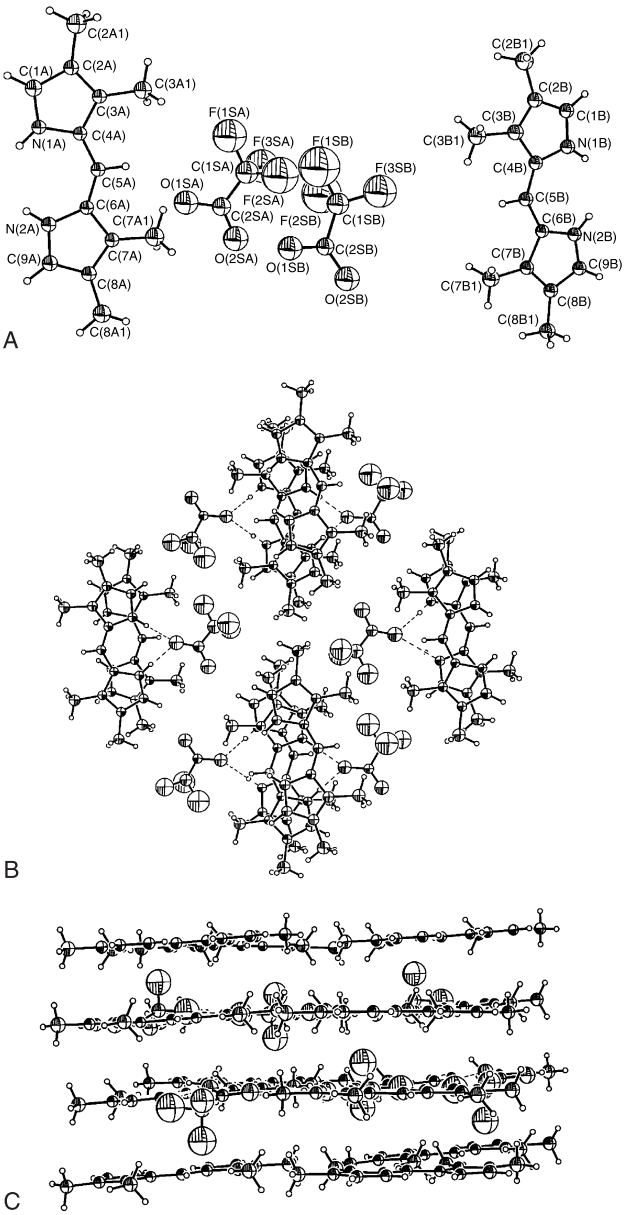


Fig. 2 (A) Crystal structure drawing of A and B molecules of **1** · *TFA* with numbering system used. Stacking pattern in face (B) and edge (C) views

The trifluoroacetate ion is located so as to coordinate its carboxylate ion with one oxygen positioned so as to coordinate equally to the two NHs of the dipyrrin · H^+ (Fig. 2). The NH···O distances are not equal: 1.88 and 1.84 Å in the A-molecule and 1.82 and 1.87 Å in the B-molecule, with corresponding unequal N–O distance of 2.76 and 2.72 Å (A-molecule) and 2.69 and 2.74 Å (B-molecule) (see Table 2). As expected for a delocalized carboxylate ion, the two C–O bond distances are 1.230/1.234 Å (A-molecule) and 1.262/1.214 Å (B-molecule).

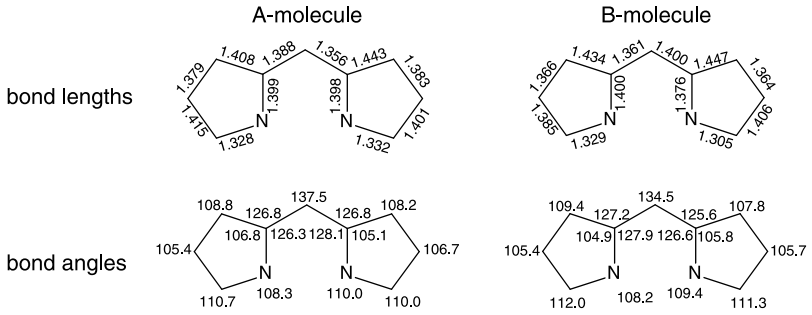


Fig. 3 Bond lengths (top row) and bond angles (bottom row) from the X-ray crystal structure of **1** · *TFA* of the (left) A-molecule and (right) B-molecule

Table 2 Key distances associated with H-bonding in the crystal of **1** · *TFA*

Distances/Å	A-molecule (N(1) and N(2))		B-molecule (N(1) and N(2))	
NH···OC(O)CF_3	1.884	1.838	1.817	1.865
NH–OC(O)CF_3	2.763	2.717	2.693	2.735
CF_3—C(=O)O	1.230	1.234	1.262	1.214

Concluding comments

A similar apparent dissymmetry was found in the crystal structure [10] of hydrobromide salt **5** (Fig. 1). The H···*Br* distances were not identical (2.30(4) and 2.23(4) Å), nor are the N–H···*Br* angles (151(4) and 167(4)°) in a pigment twisted by 13°.

Experimental

All nuclear magnetic resonance (NMR) spectra were obtained on a Varian Unity Plus spectrophotometer at 11.75 T magnetic field strength operating at a ^{1}H frequency of 500 MHz, a ^{13}C frequency of 125 MHz, and a ^{19}F frequency of 470.228 MHz in deuteriochloroform unless otherwise indicated. Chemical shifts were reported in ppm referenced to the residual chloroform proton signal at 7.26 ppm and C-13 signal at 77.23 ppm unless otherwise noted. For the ^{19}F NMR, the reference was α,α,α-trifluorotoluene at –63.72 ppm. Melting points were taken on a Mel-Temp capillary apparatus. Combustion analyses were performed by Desert Analytics, Tucson, AZ. All UV-Vis spectra were recorded on a Perkin-Elmer λ-12 spectrophotometer. Analytical thin layer chromatography (TLC) was carried out on *J.T. Baker* silica gel IB-F plates (125 μm layer). For purification, column chromatography was carried out using silica gel, 60–200 mesh (*M. Woelm*, Eschwege). All solvents were reagent grade obtained from Fisher or Acros. Deuterated chloroform and dimethylsulfoxide were from Cambridge Isotope Laboratories. Ethyl 3,4-dimethyl-1*H*-pyrrole carboxylate (**3**) [4–6, 8], 3,4-dimethyl-1*H*-pyrrolecarboxylic acid (**2**) [4], and 3,4-dimethyl-2-formyl-1*H*-pyrrole (**4**) [2, 3a] were prepared as previously reported [2a, 4].

2,3,7,8-Tetramethyl-2,2′-dipyrrin (**1**, $C_{13}H_{15}N_2$)

To 1.00 g (7.35 mmol) of 3,4-dimethyl-2-carboxy pyrrole (**2**) was added 10 cm^3 trifluoroacetic acid, and the reaction mixture was stirred for 15 min at room temperature. Triethyl orthoformate (4 cm^3, 24 mmol) was added, and the solution was stirred for 1 h. It was then added to vigorously stirred cold water (100 cm^3), and a brownish solid precipitated. It was collected by filtration and purified by column chromatography using dichloromethane as eluent. Yield: 530 mg (72%, or 47% when calculated for the trifluoroacetate salt); mp 138–140°C; ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 2.04$ (6H, s), 2.27 (6H, s), 7.21 (1H, br s), 7.62 (2H, d, $J = 2$ Hz), 11.82 (1H, br s), 12.62 (1H, br s) ppm; ^{1}H ($(CD_3)_2SO$, 500 MHz): $\delta = 2.06$, 2.35 (6H, s), 7.69 (1H, s), 8.08 (2H, s), 12.38 (2H, br s) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta = 10.1$ (C-2^1,8^1-CH_3), 10.5 (C=3^1,7^1-CH_3), 117.4 (*C*F_3CO_2H), 123.6 (C-5), 126.4 (C-3,7), 129.0 (C-4,6), 143.1 (C-1,9), 144.3 (C-2,8), 161.5 (CF_3CO_2H) ppm.

X-Ray structure and solution

Crystals of **1** · *TFA* were grown by slow diffusion of *n*-hexane into a solution of CH_2Cl_2. A crystal was placed into the tip of a 0.1 mm diameter glass capillary and mounted on a Bruker SMART Apex system for data collection at 100(2) K. A preliminary set of cell constants was calculated from reflections harvested from 3 sets of 20 frames. These initial sets of frames were oriented such that orthogonal wedges of reciprocal space were surveyed (final orientation matrices determined from global least-squares refinement of 4984 reflections. The data collection was carried out using MoKα radiation (0.71073 Å graphite monochromator) with a frame time of 20 sec for **1** and a detector distance of 4.94 cm. A randomly oriented region of reciprocal space was surveyed to the extent of 2 hemispheres and to a resolution of 0.66 Å. Four major sections of frames were collected with 0.5° steps in ω at 600 different ϕ settings and a detector position of 27° in 2θ for **1**. The intensity data were corrected for absorption and decay (SADABS) [12]. Final cell constants were calculated from the *xyz* centroids of strong reflections from the actual data collection after integration (SAINT 6.45, 2003) [13]. Crystal data and refinement information for **1** may be found in Table 3.

The structure was solved and refined using SHELXL-L [14]. The monoclinic space group $P2(1)/c$ for **1** was determined based on systematic absences and intensity statistics. A direct-

Table 3 Crystal data and structure refinement for **1** · *TFA*

Compound	
Empirical formula	$C_{15}H_{17}N_2F_3O_2$
Formula weight	314.32
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2(1)/c$
Unit cell dimensions	$a = 13.6455(4)$ Å $\alpha = 90°$ $b = 13.3439(4)$ Å $\beta = 90.625(2)°$ $c = 16.7650(6)$Å $\gamma = 90°$
Volume	3052.46(17) Å^3
Z	11
Density (calculated)	2.258 mg/m^3
Absorption coefficient	0.230 mm^{-1}
$F(000)$	2123
Crystal size	$0.36 \times 0.04 \times 0.03$ mm^3
Theta range for data collection	1.91–25.06°
Index ranges	$-15 \leq h \leq 16$, $-15 \leq k \leq 15$, $-19 \leq l \leq 19$
Reflections collected	23373
Independent reflections	5409 [R(int) = 0.0840]
Completeness to theta = 27.60°	100%
Absorption correction	None
Max. and min. transmission	0.9941 and 0.9219
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	5409/0/185
Goodness-of-fit on F^2	2.537
Final R indices [$I > 2\sigma(I)$]	$R^1 = 0.1913$, w$R^2 = 0.4563$
R indices (all data)	$R^1 = 0.2971$, w$R^2 = 0.4977$
Largest diff. peak and hole	2.490 and −1.327 eÅ^{-3}

methods solution was calculated which provided most non-hydrogen atoms from the *E*-map. Full-matrix least squares/difference *Fourier* cycles were performed for structure refinement. All non-hydrogen atoms were refined with anisotropic displacement parameters unless stated otherwise. Hydrogen atom positions were placed in ideal positions and refined as riding atoms with relative isotropic displacement parameters (a C–H distance fixed at 0.96 Å and a thermal parameter 1.2 times the host carbon atom). Tables of atomic coordinates, bond lengths and angles, anisotropic displacement parameters, hydrogen coordinates, and isotropic displacement parameters have been deposited at the Cambridge Crystallographic Data Centre, CCDC No. 670929 for **1** · *TFA*.

Acknowledgements

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