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ORIGINAL PAPER

Synthesis and Crystal Structure of Thiazole Orange Derivative

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Abstract The title compound of Thiazole Orange derivative was synthesized by the reaction of benzothiazolium and 4-methyl quinoline salts, which was determined by 1HNMR and MS. A crystalline hydrate of thiazole orange derivative was obtained when the crystal formed and characterized by single-crystal X-ray diffraction. The crystal belongs to the Triclinic system, and the cell parameters of space group P-1 were $a = 10.162(2)$ Å, $b = 10.501(2)$ Å, $c = 11.040(2)$ Å, $\alpha = 92.17(3)^{o}$, $\beta = 117.10(3)^{o}$, $\gamma = 92.28(3)^{o}$, $V = 1045.9(4)$ Å^3, $Z = 2$, $Dc = 1.380$ mg/m^{-3}, $\mu = 0.2$ mm^{-1}, $F(000) = 460$, and the final $R = 0.0625$ and $wR = 0.1862$ for 3658 observed reflections ($I > 2\sigma(I)$). The two aromatic rings linked by the methylene bridged chain are a coplanar structure.

Keywords Thiazole orange derivative · Single crystals · Characterization · Coplanar structure

Introduction

Fluorescent dyes probes have attracted much attention because of their specialities with fast detection speeds, good repeatability, low dosage, and non-radiation advantage. The cyanine dye based probe is used to detect the structures of RNA and DNA, study the remedy of damaged basic groups in DNA, identify the status of amino group and the active site of proteins, detect protein at the picomolar scale, distinguish nucleic acids with different conformations and the chemically reactive activities of related drugs [1–3].

Thiazole orange (TO), a benzothiazole ring covalently linked to a quinoline ring through a monomethine bridge, has been widely used as the embedded cyanine dye for labeling nucleic acids. The probe inserting into DNA structures by affinity is remarkable, which is due to their significant fluorescence enhancements when bound to cellular nucleic acids or to a specific surface-expressed protein partner [4] in sharp contrast to their low quantum yield in solution [5]. Design and modification fluorescent dyes can improve their application properties in the development of biological markers. So the transformation and modification of fluorescent dyes are much concerned [6] shown as below:

(1) Design, synthesis and modification of fluorescent probe molecules [7],
(2) Synthesis methods of cyanine dyes [8, 9],
(3) Targeting labeling between fluorescent probe and cancer cells [10, 11],
(4) Improvements of strength and sensitivity fluorescent dyes [12–14].

In recent years, researchers intensively investigated the modification of TO on the ring of benzothiazole or the side-chain binding with nitrogen on lepidine to improve their fluorescence intensities [15–24]. The substituent group on N of lepidine greatly affected the fluorescent properties of biomacromolecule labeled by probe. Changing the alkyl group on N of molecules can adjust the solubility and affect the aggregation behavior of dye. For example, long-chain alkyl group on N of cyanine dye can decrease or eliminate

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the crystallization caused by aggregation. Introducing proper hydrophilic substituent group onto N of lepidine can extended the application field in labeling protein.

Carboxyl group play a key role in the formation of protein and it can combine with the hydrophilic group such as amino, hydroxyl, mercapto group to form hydrogen bond, which can make the dye insert into the structure of protein. There will be a torsion in the molecular structure of dye because it may be affected by the constrain from the skelet of the protein, so the fluorescence of dye will be enhanced [25].

The fluorescent properties and the application of TO and its derivatives with carboxyl groups in biochemistry provoked us to study the crystal structure of TO derivative with carboxylic acid groups (TO-COOH).

In this article, we present our results on the synthesis and crystal growth of TO-COOH. The structure is shown in Fig. 1. The crystal of the title compound belongs to the *P*-1 space group in triclinic crystal system.

Experimental

^{1}HNMR spectra were recorded on a Bruker AC-P300 (300 MHz) spectrometer. Chemical shifts are reported in parts per million (ppm) downfield from TMS (tetramethylsilane), using DMSO-d_6 as a solvent. Mass spectral analyses were obtained using an electrospray ionization (ESI) mass spectrometer.

The dye was synthesized by a slightly modified procedure described previously [25]. The benzothiazolium was prepared via nitrogen quaternization by reacting 2-benzylmercaptobenzothiazole with methyl *p*-methyltoluenesulfonate at 110 °C for 24 h and 4-methyl quinoline salts of was synthesized from 4-methylquinoline reacting with 3-bromopropionic acid in refluxing acetone for 8 h. The dye was obtained in 97% yield by condensation of the corresponding benzothiazolium with 4-methyl quinoline salts and triethylamine (Et_3N) in ethanol at room temperature for 1 h.

To grow the crystal, the solubility of the compound was evaluated in numerous solvents such as acetone, methanol, DMF and DMSO. Its solubility in DMSO and DMF is higher compared to that in methanol and acetone. We used methanol as the solvent to grow crystal due to its moderate solubility. A saturated solution of TO-COOH in methanol at 25 °C was filtered thrice to remove suspended particles. The solution was then transferred into a beaker and allowed for slow evaporation at ambient temperature and the crystalline hydrate of TO-COOH was obtained. The resulting crystals are stable and non-hygroscopic at room temperature. 1H NMR (300 MHz, DMSO-d6): δ 2.74 (t, J = 6.45 Hz, 2H), 3.99 (s, 3H, CH_3), 4.74 (t, J = 6.10 Hz, 2H,), 6.88 (s, 1H), 7.32 (d, J = 6.9 0 Hz, 1H), 7.40 (t, J = 7.65 Hz, 1H), 7.60 (t, J = 7.80 Hz, 1H), 7.75–7.78 (m, 2H), 7.96(t, J = 7.8 Hz, 1H), 8.00(d, J =

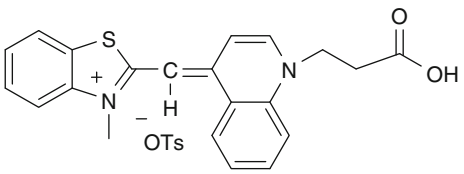

Fig. 1 Main structure of the title compound

Table 1 Crystal structure data for the title compound

Formula	$C_{21}H_{26}N_2O_6S$
Formula weight	434.50
CCDC deposit no	CCDC-739300
Temperature (K)	113(2)
Wavelength	0.71073 A
Crystal system	Triclinic
Space group	*P*-1
a (Å)	10.162(2)
b (Å)	10.501(2)
c (Å)	11.040(2)
α (°)	92.17(3)
β (°)	117.10(3)
γ (°)	92.28(3)
μ (mm^{-1})	0.2
Volume ($Å^3$)	1045.9(4)
Z	2
Calculated density (g/cm^3)	1.380
Absorption coefficient (mm^{-1})	0.196
F(000)	460
Crystal size (mm)	0.20 × 0.16 × 0.12
θ Range for data collection (°)	1.94–25.02
Index ranges	$-12 \le h \le 12$, $-12 \le k \le 12$, $-13 \le l \le 13$
Reflections collected/unique [*R*(int)]	8366/3658 [0.0358]
Completeness (%)	99.1 (to 25.02)
Refinement method	Full-matrix least-squares procedure on F^2
Weight, *w*	$1/[\sigma^2(F_o^2) + (0.1362P)^2 + 0.0230P]$, where $P = (F_o^2 + 2F_c^2)/3)$,
Data/restrains/parameters	3658/27/308
Goodness-of-fit on F^2	1.089
Final *R* indices [$I > 2$sigma(I)]	$R_1 = 0.0625$, $wR_2 = 0.1862$
R indices (all data)	$R_1 = 0.0787$, $wR_2 = 0.2079$
Max. and min. transmission	0.9769 and 0.9619
Largest diff. peak and hole (e $Å^{-3}$)	0.752 and −0.433

7.8 Hz, 1H), 8.12 (d, J = 9.00 Hz, 1H), 8.69 (d, J = 9.00 Hz, 1H), 8.77 (d, J = 9.00 Hz, 1H). ESI–MS: m/e 363.25 (M^+), 364.25 (M^++ 1).

Structure Determination and Refinement

A red crystal of the title compound having approximate dimensions of 0.20 × 0.16 × 0.12 cm^3 was mounted on the top of a glass fiber. X-ray diffraction data were collected on a Bruker Smart-1000 CCD diffractometer equipped with a graphite-monochromatized MoK_α radiation (0.7170 Å) by using an ω/φ scan mode in the range of $1.94 \leq \theta \leq 25.02°$ ($-12 \leq h \leq 12$, $-12 \leq k \leq 12$, $-13 \leq l \leq 13$) at 113(2) K. A total of 8366 reflections were collected with 3658 unique ones ($R_{int} = 0.0359$), of which 2901 with $I > 2\sigma(I)$ were observed. The structure was solved by direct methods and refined on F^2 by full-matrix least-squares procedure with SHELXS-97 and SHELXL-97 [26]. The crystal data and other structure refinement parameters of the title compound are listed in Table 1.

Results and Discussion

The selected bond lengths and bond angles are listed in Table 2, and the selected torsion angles for non-hydrogen atoms are given in Table 3. The molecular structure of the title compound is shown in Fig. 2. The crystal belongs to a crystalline hydrate with 6 crystal water. The packing diagram of the title compound in a unit cell is shown in Fig. 3. The O–H···O hydrogen bonds among the crystalloid water exist in the crystal.

The bond length of C9–C10 and C9–C8 on the bridged chain are 1.403(4) and 1.389(4) Å respectively, between the length of C–C and C=C suggesting that the delocalization of π electrons exists. The length of C9–H9 (0.9300 Å) is similar to that of aromatic hydrogen and shorter than the typical C–H. The angle of C11–C10–C9–C8 (−0.7 (5)°)indicates that C11, C10, C9, C8 are in a plane. In the meanwhile we find that the angles of C18–C10–C9–C8 and C9–C10–C18–C13 are 179.3 (3)° and −179.3 (3)° respectively, which indicate that C18, C13, C10, C9, C8 are in a plane. So, quinoline ring is planar with

Table 2 Selected bond lengths (Å) and bond angles (°)

Bond	Dist.	Bond	Dist.	Bond	Dist.
S(1)–C(1)	1.731(3)	C(10)–C(11)	1.399(4)	N(2)–C(19)	1.499(4)
S(1)–C(8)	1.740(3)	C(10)–C(9)	1.403(4)	C(21)–(20)	1.537(4)
O(1)–C(21)	1.237(4)	C(10)–(18)	1.462(4)	C(17)–C(16)	1.352(5)
N(1)–C(8)	1.368(4)	C(9)–C(8)	1.389(4)	C(20)–C(19)	1.499(5)
N(1)–C(6)	1.393(4)	C(9)–H(9)	0.9300	C(13)–C(14)	1.396(5)
N(1)–C(7)	1.461(4)	N(2)–C(12)	1.336(4)	C(11)–(12)	1.377(4)
O(2)–C(21)	1.261(4)	N(2)–C(13)	1.392(4)	C(16)–C(15)	1.407(5)
Angle	(°)	Angle	(°)	Angle	(°)
C(8)–N(1)–C(6)	115.0(2)	C(11)–C(10)–C(9)	124.7(3)	C(8)–C(9)–C(10)	128.7(3)
C(8)–N(1)–C(7)	122.1(2)	C(11)–C(10)–C(18)	114.7(3)	C(8)–C(9)–H(9)	115.6
C(6)–N(1)–C(7)	122.9(2)	C(9)–C(10)–C(18)	120.6(3)	C(10)–C(9)–H(9)	115.6
N(1)–C(8)–C(9)	122.1(3)	C(12)–N(2)–C(13)	120.0(3)	C(13)–C(18)–C(17)	116.5(3)
N(1)–C(8)–S(1)	110.2(2)	C(12)–N(2)–C(19)	118.0(3)	C(13)–C(18)–C(10)	121.0(3)
C(9)–C(8)–S(1)	127.6(2)	C(13)–N(2)–C(19)	121.9(3)	C(17)–C(18)–C(10)	122.6(3)

Table 3 Selected torsion angles (°)

Angle	(°)	Angle	(°)	Angle	(°)
C11–C10–C9–C8	−0.7(5)	O1–C21–C20–C19	179.8(3)	C7–N1–C8–S1	178.3(2)
C18–C10–C9–C8	179.3(3)	O2–C21–C20–C19	−0.7(4)	C10–C9–C8–N1	179.6(3)
C9–C10–C18–C13	−179.3(3)	C6–N1–C8–C9	179.8(3)	C10–C9–C8–S1	−0.6(5)
C9–C10–C18–C17	1.5(4)	C7–N1–C8–C9	−1.8(5)	C1–S1–C8–C9	179.6(3)

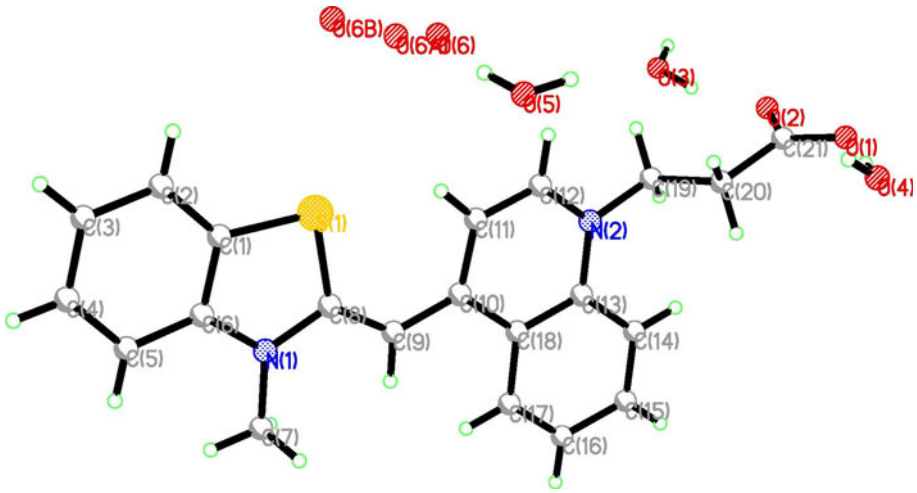

Fig. 2 X-ray crystal structure of the title compound

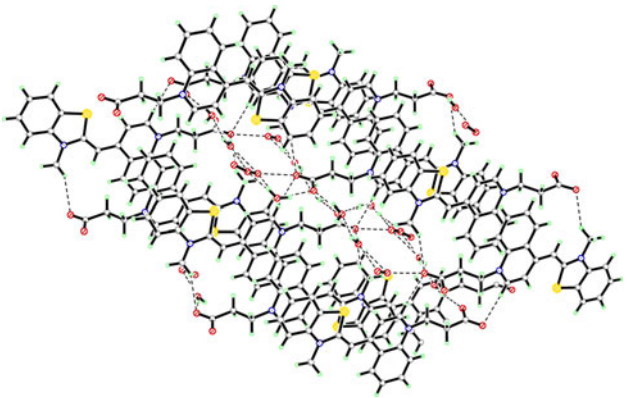

Fig. 3 A packing diagram for the title compound

the C11–C9–C8–C10. On the other hand, the angles of C6–N1–C8–C9 (179.8(3)°), C10–C9–C8–N1 (179.6(3)°), C10–C9–C8–S1 (−0.6(5)°), C1–S1–C8–C9 (179.6(3)°) show that C10, C9, C8, N1, S1, C1, C6 are in a plane. According to the angles' parameters, it is released that C11, C9, C8, C10, C13, C18, C10, C9, C8, N1, S1, C1, C6 are in the same plane. So, the two aromatic rings are coplanar structure linked by the methylene bridged chain from the selected torsion angles. The reaction of benzothiazolium and 4-methyl quinoline salts with triethylamine give the title compound bearing the methylene bridged chain. The structure elucidation was achieved by X-ray diffraction, and proved cleanly that the reaction occurs to form the title compound.

Supplementary Material

CCDC 739300 contains the supplementary crystallographic data for this article. This data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, by e-mailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(0)1223-336033.

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