Dyes and Pigments 94 (2012) 490-495

ELSEVIER

Contents lists available at SciVerse ScienceDirect

Dyes and Pigments



journal homepage: www.elsevier.com/locate/dyepig

# Unsymmetric leuco-TAM dyes, (2*E*, 2'*E*)-2,2'-{(E)-4-phenylpent-2-ene-1,5diylidene}bis(1,3,3-trimethylindoline) derivatives. Part II: X-ray crystal structure<sup> $\Rightarrow$ </sup>

Sam-Rok Keum\*, So-Young Ma, Do-Kyung Kim, Hyun-Woo Lim, Se-Jung Roh

Department of Advanced Materials Chemistry, Korea University, Se-Jong Campus, Jochiwon, ChoongNam 339-700, South Korea

# A R T I C L E I N F O

Article history: Received 23 November 2011 Received in revised form 17 January 2012 Accepted 10 February 2012 Available online 16 February 2012

Keywords: Unsymmetrical leuco-TAM Unsymmetric three-bladed propeller conformation *EEE* isomers Stereoselective formation Near-IR dyes Cy5 TAM<sup>+</sup> dye

# ABSTRACT

The unequivocal solid-state structure and stereochemistry of the unsymmetric leuco-triarylmethane (Un-LTAM) dye 2,2'-{(E)-4-(phenyl)pent-2-ene-1,5-diylidene}bis(1,3,3-trimethylindoline) derivatives were established using X-ray single-crystal analysis. The X-ray analysis showed that the *EEE* isomers were formed stereoselectively with an unsymmetric three-bladed propeller conformation from the reaction of a Fischer's base and cinnamaldehyde derivatives. The 5,5'-dichloro-4"-nitro-triarylmethane dye displayed a triclinic crystal structure with the space group *P-1*. The molecules stack alternately to form a dimer, adopting intermolecular distances of 8.53 and 9.40 Å for rings B and C, respectively. Unsymmetric triarylmethane cations, the oxidized form of these dyes, have UV absorptions over 680 nm and selected examples absorb close to the near-IR region.

© 2012 Elsevier Ltd. All rights reserved.

# 1. Introduction

Triarylmethane (TAM) compounds, sometimes referred to as "Leuco-TAM (LTAM) molecules," are precursors of the TAM<sup>+</sup> dyes [1–4]. A number of TAM<sup>+</sup> dyes such as malachite green (MG), crystal violet, and pararosaniline are well known. These dyes have potential in numerous applications in the chemical and lifesciences industries, such as ink dyes, thermal imaging, carbonless copying materials, and drugs [5,6]. They are also widely used in pharmaceutical and medicinal applications, such as photo-chemotherapy agents and particularly in eye-protection devices [7,8]. In addition, triarylmethyl (trityl) cations are stabilized by the resonance effect of the phenyl rings, and they have become useful as protective groups, especially in nucleoside chemistry [9]. Trityl groups generating cations of different colors have thus been used to protect different nucleotides in oligonucleotide synthesis [10,11].

Among the abovementioned TAM<sup>+</sup> dyes, MG is one of the most commonly used chemicals in dye chemistry. Significant quantities of MG and related triarylmethane dyes are produced annually for this purpose [12]. MG is known to be absorbed by the human body in other forms such as carbinol and leuco forms. MG is very active against the fungus Saprolegnia, which infects fish eggs in commercial aquaculture, and is also known to be a good treatment against ichthyophthirius in freshwater aquaria. However, the principal metabolite, leuco-MG (LMG), is found in fish treated with MG, and this finding has been the subject of controversy and government regulation. The use of this substance has thus been restricted in many countries [13,14].

A number of research groups [15–17], including us [18–20], have thus investigated structural modifications of LTAM molecules. Significant progress has thus been made toward the synthesis of novel LTAM/TAM<sup>+</sup> dyes. Very recently, we reported [21] the synthesis of unsymmetrical LTAM (2*E*,2′*E*)-2,2′-{(*E*)-4-phenylpent-2-ene-1,5-diylidene}bis(1,3,3-trimethylindoline) derivatives obtained from the reaction of an excess Fischer's base (FB) and substituted cinnamaldehydes. The chemical structures of these molecules in solution, determined tentatively by <sup>1</sup>H and <sup>13</sup>C NMR spectroscopy using 1D and 2D techniques, were found to be precursors of a Cy5 TAM<sup>+</sup> dye [22]. The Cy5 TAM<sup>+</sup> dye is a potent near-IR heptamethine cyanine dye, which is a promising imaging agent for human cancers, and can be further exploited to improve cancer detection, prognosis, and treatment [23].

The unsymmetrical LTAM molecules (Un-LTAM) in the solid state can be characterized by unambiguous structural and stereochemical elucidation. The Un-LTAM molecules consist of a methane molecule with three aromatic groups such as 2-allyidene-1,3,3-

<sup>☆</sup> Part I. Ref. 21.

<sup>\*</sup> Corresponding author. Tel.: +82 41 860 1332; fax: +82 41 867 5369. *E-mail address*: keum@korea.ac.kr (S.-R. Keum).

<sup>0143-7208/\$ –</sup> see front matter @ 2012 Elsevier Ltd. All rights reserved. doi:10.1016/j.dyepig.2012.02.007



Scheme 1. Chemical structures of Un-LTAM molecules.

trimethylindolinyl (A), 1,3,3-trimethyl-2-methyleneindolinyl (B), and a phenyl (C) ring, as shown in Scheme 1.

To the best of our knowledge, the X-ray crystal analysis of Un-LTAM bearing two different types of 2-methyleneindoline (FB) moieties has not yet been described in the literature. This work describes the solid-state structure of the Un-LTAM molecule.

# 2. Materials and methods

# 2.1. General procedures

The melting points were determined on a Fischer–Johns block and were not corrected for. The <sup>1</sup>H NMR spectra were acquired using a Bruker CXP-300 FT-NMR spectrophotometer. The electronimpact mass spectra were recorded on a VG Quattro mass spectrometer at Queen's University, Kingston Canada.

# 2.2. Materials

The required 2-methylene-1,3,3-trimethylindoline (FB), 5-chloro-2-methylene-1,3,3-trimethylindoline, trans-cinnamaldehyde, and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) were purchased from Aldrich Chemical Co. and were used without further purification.

An excess of FB was added dropwise to an ethanolic solution of cinnamaldehyde. The reaction mixture was stirred in an ice bath for 5–6 h. The precipitate was filtered, washed thoroughly with cold ethanol, and purified by precipitation from acetone/hexane. Detailed synthetic procedures for the Un-LTAM molecules are described elsewhere [18]. The TAM<sup>+</sup> was obtained from a reaction of Un-LTAM molecule with DDQ in the presence of HCl, followed by separation of deep blue colored form from the product mixtures by column chromatograph in MC/MeOH (7:1). TAM<sup>+</sup> was then converted into the carbinol in base (NaOH). Decomposed product {5-chloro-1,3,3-trimethyl-2-((1E,3E)-4-(4-nitrophenyl)buta-1,3-dienyl)indolium perchlorate} was isolated from the reaction of Un-LTAM 4 with HClO<sub>4</sub>.

**5-chloro-1,3,3-trimethyl-2-((1E,3E)-4-(4-nitrophenyl)buta-1,3-dienyl)indolium perchlorate**, brown, Yield 57%, M.p. = 257–258 °C, ir (KBr) 3072, 2984, 2934, 1707, 1596, 1340 and 1086 cm<sup>-1, 1</sup>H NMR (DMSO- $d_6$ )  $\delta$  1.76 (6H, s), 4.03 (3H, s), 7.37 (1H, d, *J* = 15.3 Hz), 7.66 (1H, dd, *J* = 10.2, 15.3 Hz), 7.73 (1H, d, *J* = 9.0 Hz), 7.79 (1H, d, *J* = 15.3 Hz), 7.92 (2H, d, *J* = 6.9 Hz), 7.95 (1H, d, *J* = 9.0 Hz), 8.09 (1H, s), 8.33(1H, dd, *J* = 10.2, 15.3 Hz), 8.33(2H, d, *J* = 6.9 Hz).

#### 2.3. X-ray crystallography

Crystal data for Un-LTAM **4**  $[C_{33}H_{33}N_3Cl_2O_2]$ , M = 574.52, triclinic, a = 11.1280(17), b = 11.7321(18), c = 13.808(2) Å, U = 1514.7(4) Å, T = 293(2) K, space group *P*-1, Z = 2,  $\mu$ (Mo-K $\alpha$ ) = 0.248 mm<sup>-1</sup>, 20,744 reflections measured, and 7485 unique (R(int) = 0.0297) were used in all calculations. The final  $wR(F^2)$  was 0.1504. The intensity data for Un-LTAM **4** were collected using a Siemens SMART CCD area detector mounted on a Siemens P4 diffractometer equipped with a graphite-monochromated Mo-K $\alpha$ 

radiation source ( $\lambda = 0.71073$  Å) and a CCD detector. All multiframes of the two-dimensional diffraction images were collected. The frame data were processed to determine the structural factors using the program SAINT [24]. The structure was found using direct methods and refined with full-matrix least-squares on  $F^2$  for all of the data using the SHELXTL software [25]. The hydrogen atom positions were initially determined geometrically and refined using a Dreiding model. The non-hydrogen atoms were refined using anisotropic displacement parameters.

# 2.4. UV-vis spectroscopy

UV—vis absorption spectra were recorded using a Varian Cary 1E UV—visible spectrometer, and IR spectra were recorded using an Analet Instrument FT-IR (MAP-60) using KBr pellets.

Stock solutions  $(2.05 \times 10^{-5} \text{ M})$  of Un-LTAM **1–4** in DMF were made in 5 mL volumetric flasks in an inert atmosphere. The flasks were then capped with a rubber septum, wrapped in aluminum foil, and stored at 0 °C. Reproducible results of the acid-catalyzed transformation of LTAM dye to cyanine dye were obtained using a protocol that maximized the formation of the colored form. Briefly, 3 mL of the selected organic solvent was injected into a 1cm-path-length quartz cuvette. The cuvette was then placed in the thermostated (25 °C) cell compartment of a UV–vis spectrophotometer. The absorption maxima in the UV–vis spectra were obtained from the final absorption scans of the colored cyanine forms of the Un-LTAM molecules.

# 3. Results and discussion

Table 1

Un-LTAM dyes **1**–**4** were prepared by the reaction of the FB, 2methylene-1,3,3-trimethylindoline, with substituted cinnamaldehydes in a 2.5:1 ratio in ethanol, in a modification of the known method [18].

The stereochemistry of the diastereomer of the prepared LTAM molecules in organic solvents was tentatively determined using <sup>1</sup>H NMR and 2D NMR techniques. The *EEE* isomer was obtained as the major product in all of the cases examined. For no apparent reason, the other diastereomers could not be isolated in the solid state. This

Crystal data and structural refinement for Un-LTAM **4**.

Identification code	Un-LTAM <b>4</b>
Empirical formula	C <sub>33</sub> H <sub>33</sub> Cl <sub>2</sub> N <sub>3</sub> O <sub>2</sub>
Formula weight	574.52
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system, space group	Triclinic, <i>P</i> -1, <i>R</i> = 0.0558
Unit cell dimensions	$a = 11.1280(17)$ Å, $\alpha = 114.033(3)^{\circ}$
	$b = 11.7321(18)$ Å, $\beta = 93.314(3)^{\circ}$
	$c = 13.808(2)$ Å, $\gamma = 109.293(3)^{\circ}$
Volume	1514.7(4) Å <sup>3</sup>
Z, Calculated density	2, 1.260 Mg/m <sup>3</sup>
Absorption coefficient	$0.248 \text{ mm}^{-1}$
F(000)	604
Crystal size	$0.30 \times 0.20 \times 0.20 \text{ mm}$
Theta range for data collection	1.66-28.30°
Limiting indices	$-14 \le h \le 14$ , $-15 \le k \le 15$ , $-18 \le l \le 18$
Reflections collected/unique	20,744/7485 [ <i>R</i> (int) = 0.0297]
Completeness to theta $=$ 28.30	99.4%
Max. and min. transmission	0.9520 and 0.9293
Refinement method	Full-matrix least-squares on F <sup>2</sup>
Data/restraints/parameters	7485/0/367
Goodness-of-fit on F <sup>2</sup>	1.043
Final R indices $[I > 2 \text{sigma}(I)]$	R1 = 0.0558, $wR2 = 0.1504$
R indices (all data)	R1 = 0.0912, $wR2 = 0.1738$
Largest diff. peak and hole	0.338 and -0.389 e Å <sup>-3</sup>

Table 2		
Selected bond distances	(Å), and bond	angles (°) for 4

Ring <sup>a</sup>	Bond distances		Bond angles			
	Bond	Distances (Å)	Bond	Angles (°)		
A	N(1)-C(2) N(1)-C(10) C(2)-C(7")	1.397 1.439 1.345	C(2)-N(1)-C(7a) C(2)-N(1)-C(10) C(2)-C(7")-H(7") C(7")-C(2)-N(1) C(7")-C(2)-C(3)	111.66 123.9 117.1 123.8 128.67		
В	N(2)-C(2') N(2)-C(10') C(2')-C(11")	1.408 1.445 1.324	$\begin{array}{l} C(2')-N(2)-C(7a') \\ C(7a')-N(2)-C(10') \\ C(2')-N(2)-C(10') \end{array}$	111.32 124.45 123.11		
Connecting group	C(1")-C(10") C(9")-C(10") C(10")-C(11") C(8")-C(9") C(7")-C(8")	1.516 1.516 1.509 1.328 1.443	$\begin{array}{c} C(9'')-C(10'')-C(11'')\\ C(1'')-C(10'')-C(11'')\\ C(9'')-C(10'')-C(11'')\\ C(8'')-C(9'')-C(10'')\\ C(11'')-C(2')-C(10'')\\ C(11'')-C(2')-C(3')\\ C(2')-C(11'')-H(11'')\\ C(8'')-C(9'')-H(9'')\\ C(10'')-C(9'')-H(9'')\\ C(10'')-C(9'')-H(9'')\\ C(9'')-C(8'')-H(8'')\\ C(9'')-C(8'')-H(8'')\\ C(7'')-C(8'')-H(8'')\\ C(7'')-C(8'')-H(8'')\\ C(2')-C(7'')-C(8'')\\ C(8'')-C(7'')-H(7'')\\ C(2')-C(11'')-C(10'')\\ C(10'')-C(11'')-H(11'')\\ \end{array}$	110.92 110.01 110.92 127.29 122.42 130.02 115.6 116.4 116.4 125.0 117.5 117.5 125.8 117.1 128.78 115.6		

<sup>a</sup> Symbols (rings A and B) are denoted as indicated in Scheme 1.

is somewhat surprising because the *ZE*-isomers are formed stereoselectively for the FB-analogs of LTAM molecules in both solid and solution states, as reported previously [18,19].

The Un-LTAM **4** compound was the only compound that gave crystals (from acetone) suitable for X-ray analysis. Unfortunately, crystal growth was unsuccessful for the remainder of the Un-LTAM molecules. Table 1 shows the crystal data, structural refinement,



Fig. 2. Propeller shape of Un-LTAM 4, showing the interplanar angles.

atomic coordinates (×10<sup>4</sup>), and equivalent isotropic displacement parameters ( $Å^2 \times 10^3$ ) for **4**. The selected bond lengths and bond angles are listed in Table 2.

X-ray crystal structures of the Un-LTAM dye **4** showed a triclinic crystal system with the space group *P-1*. An ORTEP diagram of **4**, including the atom-numbering scheme, is shown in Fig. 1.

The C(9")-C(10") and C(10")-C(11") distances are 1.516 and 1.509 Å, respectively, which are typical C–C single bond lengths. The single bond C(7")–C(8") distance, however, was 1.443 Å, which is shorter than typical C–C single bond lengths and longer than those typical for C–C double bonds, and is perhaps due to conjugation. It is known that the length (1.47 Å) of the central single bond of 1,3-butadiene is approximately 6 Å shorter than that of the analogous single bond (1.53 Å) in butane. The two enamine C(2)–C(7") and C(2')–C(11") bond lengths, and the C(8")–C(9") double bond length were 1.354, 1.324 and 1.328 Å, respectively, which are typical C=C bond lengths.

In the crystals, the three aromatic rings of **4** were linked to three different layers, *viz.* a vinyl FB (ring A), a FB (ring B), and a phenyl group. The unsymmetrical molecule is a distorted version of the well-known three-bladed propeller conformation [18,19]. The interplanar angles of the aromatic rings A–B, A–C, and B–C are  $87.4^{\circ}$ ,  $67.5^{\circ}$  and  $61.5^{\circ}$  for **4**, as shown in Fig. 2.

The dihedral angle ( $\theta$ ) of H10"-C10"-C11"-H11" was 170.9° for **4**, in the solid state. For a representative comparison, the value was



Fig. 1. ORTEP diagram of Un-LTAM 4, showing the atom-numbering scheme.

Table 3	
Interplanar angles and dihedral angles (	°) for Un-LTAM 1-4.

Names	Compounds <sup>a</sup>		Interplanar angles <sup>b</sup> (°)			Dihedral angle <sup>c</sup>	Note <sup>d</sup>	
	Aryl <sup>A</sup>	Aryl <sup>B</sup>	Aryl <sup>C</sup>	Ring A–B	Ring B–C	Ring C–A	<i>θ</i> (°)	
Bis-(FB)PP <sup>e</sup>	Н	Н	Н	79.8	74.9	84.8	164.1	Exp
Bis-(5-ClFB)PPe	5-Cl	5-Cl	Н	60.1	75.7	83.2	178.9	Exp
Un-LTAM 1	5-Cl	5-Cl	Н	_	_	_	162.0	Calc
Un-LTAM 2	Н	Н	$4-NO_2$	_	-	_	163.0	Calc
Un-LTAM 3	5-Cl-7-	5-Cl-7-	$4-NO_2$				166.0	Calc
	$NO_2$	$NO_2$						
Un-LTAM 4	5-Cl	5-Cl	$4-NO_2$	_	_	_	162.0	Calc
Un-LTAM 4	5-Cl	5-Cl	$4-NO_2$	87.4	61.5	67.5	170.9	Exp

<sup>a</sup> Symbols (Aryl<sup>A, B & C</sup>) are in the order of *Z*-FB ring, *E*-FB ring and phenyl rings for the LTAM, and vinylated FB, FB & phenyl rings for Un-LTAM, respectively.

<sup>b</sup> Symbols (A–B) and numbering systems are denoted as indicated in Scheme 1.

<sup>c</sup> Symbol (θ) is denoted a dihedral angle of H10"-C10"-C11"-H11". <sup>d</sup> Exp and calc denote experimental and calculated values, respectively.

<sup>e</sup> Symbols are abbreviations for the symmetric LTAM (FB-analogs of MG) as in ref. 18.

calculated using the modified Karplus relationship between coupling constants and dihedral angles [26,27]. The calculated value (162° for  $\theta$ ) is compared with the experimental one (170.9°); these values are in reasonable agreement. This indicates that the modified Karplus equation is acceptable for the  $\theta$  values of the Un-LTAM molecules, as is the case for the symmetric LTAM dyes [19]. The dihedral angles of the other three molecules **1–3** in the solution state were calculated using the modified Karplus equation from the <sup>1</sup>H NMR vicinal coupling-constant values. The calculated and experimental values of interplanar and dihedral angles for **1–4** are given in Table 3.

The double bonds C(2)=C(7''), C(8'')=C(9''), and C(2')=C(11'') of Un-LTAM **4** have *EEE* configurations. The *EEE* isomers of these LTAM dyes are formed as the sole product in all cases, even though there are three possible isomers, the two other diastereomers being

 Table 4

 UV-vis spectral data of various forms of Un-LTAM 1-4.

Compounds <sup>a</sup>	Various	Various structural forms <sup>b</sup> ( $\lambda_{max}$ )				
	Leuco-	Carbinol-	TAM <sup>+</sup> - (c) <sup>c</sup>		Conjugated	
	(a)	(b)	x-Band	y-Band	dye (d)	
Crystal violet <sup>d</sup>	265	266	585	-	_	Blue violet
Malachite green <sup>e</sup>	265	265	620	430	_	Green
Bis-(FB)PP <sup>f</sup>	284	343	609	426	385	Blue
Bis-(5-ClFB)PP <sup>f</sup>	296	327	578	370	391	Blue
Un-LTAM 1	322	381	693	412	420	Green
Un-LTAM 2	326	383	686	414	415	Green
Un-LTAM 3	324	368	686	353	435	Green
Un-LTAM 4	326	374	704	417	425	Green

<sup>a</sup> Names of compounds are the same as in Table 3.

<sup>b</sup> Symbols (a)–(d) are as indicated in Fig. 6.

<sup>c</sup> Symbols (*x*-, *y*-band) are adopted from ref. 22.

<sup>d</sup> Data for acetonitrile from ref. 26.

<sup>e</sup> Data for acetonitrile from ref 29

<sup>f</sup> Data in chloroform from refs. 18,19.

the ZEE and ZEZ isomers (Fig. 3). The central carbon–carbon double bonds of these LTAM dyes are generally expected to have an E configuration.

Although the presence of the ZEE and ZEZ diastereomers was generally expected to be found in organic solvents, none of these isomers were detected, unlike for the LTAM molecules examined previously [20]. Diastereomeric isomerization between *EEE* and *EEZ* forms of these Un-LTAM molecules are not detected in organic solvents. Either the geminal dimethyl or N-methyl groups of ring B locates in a proximity of the phenyl group, depending on the configuration of the ring B. Thus, diastereomeric discrimination is now possible only from the <sup>1</sup>H NMR resonances of the geminal dimethyl or N-methyl groups of ring B. Selected <sup>1</sup>H NMR data for the Un-LTAM molecules **1**–**4** are collected and listed in Table 4. The stereoselective formation of the *EEE* isomer of these dyes from the reaction of an excess FB and cinnamaldehydes requires further study.



Fig. 3. Structures of ZEE and ZEZ diastereomers.



Fig. 4. Molecular packing diagram of Un-LTAM 4 showing dimer formation.

The distance between the ortho-proton, H2"/H6", in the phenyl ring and gem-methyl protons, H8'/H9', of the FB (B) ring is 5.221 Å, whereas it is 4.840 Å for the gem-methyl protons, H8/H9, of the FB (A) ring. This is the reason why a local diamagnetic anisotropy could be detected only for the former by <sup>1</sup>H NMR spectroscopy [18], although both FB rings have the *E* configuration. This situation would further explain the collapse of the N-methyl peaks at 3.00 ppm of the A and B rings. However, local diamagnetic anisotropy was not detected because Un-LTAM has no FB unit having a *Z*-configuration.

Compound **4** is stacked in an alternating fashion to form a dimer in the unit cell of the crystal. Fig. 4 shows the molecular packing diagram of Un-LTAM **4**, showing the formation of the dimer. The intermolecular distances in the dimer are 8.53 and 9.40 Å, for the rings B and C, respectively.

The colored forms (c) were obtained from the reaction of the Un-LTAM materials with DDQ/HCl. The colored forms, TAM<sup>+</sup>, of the prepared LTAM molecules have absorption maxima at 412-419 and 679-704 nm in ethanol, and the carbinol form (b) was detected at 360-380 nm in basic media. The leuco form of these molecules decomposed in HCl-saturated EtOH to form conjugated molecules (d) observed at 415-420 nm.



**Fig. 5.** UV–vis spectral data for Un-LTAM **4** in EtOH showing the various forms such as the leuco (a, solid), TAM<sup>+</sup> (b, dash-dot-dot), carbinol (c, dash-dot), and decomposed forms (d, dash).

UV-vis spectral data in EtOH shows various structural forms of the Un-LTAM **4**, such as (a) leuco, (b) colored TAM<sup>+</sup>, (c) carbinol and (d) decomposed forms, similar to the TAM dyes. These spectra are shown in Fig. 5.

From the reaction of Un-LTAM 4 with HClO<sub>4</sub>, a decomposed product  $\mathbf{d}$  was isolated, whose chemical structure is shown in Scheme 2.

The chemical structure of the decomposed dye structure **d** has been determined by <sup>1</sup>H NMR and 2D COSY experiment. <sup>1</sup>H $^{-1}$ H COSY was used to identify protons belonging to the central protons, H11 $^{-}$ H14, linking the two aromatic rings. The COSY in the range of 7.0–8.5 ppm showed three correlation [H11 $^{-}$ H12, H12 $^{-}$ H13, H13 $^{-}$ H14] for the central protons of the decomposed product.

A measure of the electronic effect of the FB group was obtained from the spectrum of the FB analog of MG. A hypsochromic shift ( $\sim$  20 nm) of the *x*-band of the FB analog dyes was observed relative to MG itself, whereas, a pronounced bathochromic shift ( $\sim$  100 nm) of the *x*-band was observed relative to MG. It is assumed that the pronounced bathochromic shift is associated with the extended conjugation [28] in the chain branch that includes ring A. All of the prepared Un-TAM<sup>+</sup> dyes **1–4** showed absorption maxima at longer wavelengths, namely the *x*-band of the Un-TAM molecules, than those of the well-known MG dyes. UV—vis spectral data for various forms of Un-LTAM **1–4**, compared to those of the well-known TAM<sup>+</sup> dyes, are summarized in Table 4.

In the UV–vis measurements, MG exhibits absorption maxima at 620 and 430 nm for the *x*- and *y*-bands, respectively. On the other hand, the absorption maxima of the vinylog of MG are red-shifted for both *x*- and *y*-bands, viz. at 651 and 488 nm, respectively. This observation suggests that the vinyl effects of a vinyl unit may be like those due to extended conjugation for both *x*- and *y*-bands, to a large extent. Chemical structures for various TAM<sup>+</sup> dyes are shown in Fig. 6 for the N ~ N<sup>+</sup> and C(phenyl) ~ N<sup>+</sup> responsible for the *x*- and *y*-bands, respectively.





Scheme 2. Chemical structure of the decomposed product d.



Fig. 6. Chemical structures for the N ~ N<sup>+</sup> and C(phenyl) ~ N<sup>+</sup> responsible for the x- and y-bands, respectively, in the UV-vis measurements.

# 4. Conclusions

The unequivocal solid-state structure and stereochemistry of novel Un-LTAM,  $(2E,2'E)-2,2'-\{(E)-4-phenylpent-2-ene-1,5-diylidene\}bis(1,3,3-trimethylindoline) derivatives were established using X-ray single-crystal analysis. The X-ray crystal analysis showed that the$ *EEE*isomers formed stereoselectively, unlike the previously reported symmetric*ZE*-LTAM FB-analogs of MG. UV data for these Un-TAM<sup>+</sup> dyes showed absorption in the near-IR region (~700 nm). The pronounced bathochromic shift is presumably associated with the extended conjugation effect of ring A in the Un-TAM<sup>+</sup> dyes.

# Acknowledgments

This work was supported by the Korea Research Foundation grant funded by the Korea government (MEST) (No. 2009-0071425) and partly by the Brain Korea 21 project.

# Supplementary material

The crystallographic data for the structural analysis was provided to the Cambridge Crystallographic Data Center as a supplementary publication number CCDC 851595 for **4**. A copy of this information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk).

# References

- Balko L, Allison J. The direct detection and identification of staining dyes from security inks in the presence of other colorants, on currency and fabrics, by laser desorption mass spectrometry. J Forensic Sci 2003;48:1172–8.
- [2] Kumar D, Singh AC, Usha PN, Tandon R, Triphathi K. Primary amyloidosis presenting with predominant lymphnodal masses. J Assoc Physicians India 2005;53:312–3.
- [3] Kher AA, Green EV, Mulholland MI. J Forensic Sci 2001;46:878.
- [4] Nair V, Thomas S, Mathew SC, Abhilash KG. Recent advances in the chemistry of triaryl- and triheteroarylmethanes. Tetrahedron 2006;62:6731–47.
- [5] Fabian J, Hartmann H. Light absorption of organic colorants. Berlin-–Heidelberg–New York: Springer; 1980.
- [6] Rys P, Zollinger HH. Farbstoffchemie. Weinheim: Verlag Chemie; 1982.
- [7] Indig GL, Anderson GS, Nichols MG, Bartlett JA, Mellon WS, Sieber F. Effect of molecular structure on the performance of triarylmethane dyes as therapeutic agents for photochemical purging of autologous bone marrow grafts from residual tumor cells. J Pharm Sci 2000;89:88–99.

- [8] Lurtz MM, Pedersen SE. Aminotriarylmethane dyes are high-affinity noncompetitive antagonists of the nicotinic acetylcholine receptor. Mol Pharmacol 1999;55:159–67.
- [9] Greene TW, Wuts PGM. Protective groups in organic synthesis. USA: Wiley; 1991.
- [10] Gildea BD, Coull JM, Köster H. Tetrahedron Lett 1990;31:7095-8.
- [11] Coull JM, Gildea B, KoÈster H. Succinimidyl trityl compounds and a process for preparing same. Patent USA 5,410,068; 1995.
- [12] Gessner T, Mayer U. Triarylmethane and diarylmethane dyes, Ullmann's encyclopedia of industrial chemistry. Weinheim: Wiley-VCH; 2002.
- [13] Cho BP, Yang T, Lonnie R, Blankenship L, Moody JD, Churchwell M, et al. Chem Res Toxicol 2003;19:285.
- [14] Culp SJ, Beland FA, Heflich RH, Benson RW, Blankenship LR, Webb PJ, et al. Mutat Res 2002;506:55–63.
- [15] Nair V, Abhilash KG, Vidya N. Practical synthesis of triaryl- and triheteroarylmethanes by reaction of aldehydes and activated arenes promoted by gold(III) chloride. Org Lett 2005;7:5857–9.
- [16] Podder S, Choudhury J, Roy UK, Roy S. Dual-reagent catalysis within Ir–Sn domain: highly selective alkylation of arenes and heteroarenes with aromatic aldehydes. J Org Chem 2007;72:3100–3.
- [17] Liu C-R, Li M-B, Yang C-F, Tian S-K. Catalytic selective bis-arylation of imines with anisole, phenol, thioanisole and analogues. Chem Commun; 2008:1249–51.
- [18] Keum SR, Roh SJ, Lee MH, Saurial F, Buncel E. <sup>1</sup>H and <sup>13</sup>C NMR assignments for new heterocyclic TAM leuco dyes, (2Z,2'E)-2,2'-(2-phenyl propane-1,3diylidene)bis(1,3,3-trimethylindoline) derivatives. Part II. Magn Reson Chem 2008;46:872-7.
- [19] Keum SR, Roh SJ, Kim YN, Im DH, Ma SY. X-ray crystal structure of hetaryl leuco-TAM dyes, (2Z,2'E)-2,2'-(2-phenylpropane-1,3-diylidene) bis(1,3,3trimethyl indoline) derivatives. Bull Korean Chem Soc 2009;30:2608–12.
- [20] Keum SR, Roh SJ, Ma SY, Kim DK, Cho AE. Diastereomeric isomerization of hetaryl leuco-TAM dyes, (2Z, 2'E)-2,2'-(2-phenyl propane-1,3-diylidene) bis(1,3,3-trimethylindoline) derivatives in various organic solvents. Tetrahedron 2010;66:8101-7.
- [21] Keum SR, Lee MH, Ma SY, Kim DK, Roh SJ. Novel unsymmetrical leuco-TAM, (2E, 2'E)-2,2'-{(E)-4-phenylpent-2-ene-1,5-diylidene}bis(1,3,3-trimethylindoline) derivatives: synthesis and structural elucidation. Dyes Pigm 2011;90: 233–8.
- [22] Ernst LA, Gupta RK, Mujumdar RB, Waggoner AS. Cyanine dye labeling reagents for sulfhydryl groups. Cytometry 1989;10:3–10.
  [23] Yang X, Shi C, Tong R, Qian W, Zhau HE, Wang R, et al. Near IR heptamethine
- [23] Yang X, Shi C, Tong R, Qian W, Zhau HE, Wang R, et al. Near IR heptamethine cyanine dye-mediated cancer imaging. Clin Cancer Res 2010;16(10):2833-44.
- [24] SMART & SANIT software reference manuals, version 4.0. Madison, Wisconsin, USA: Siemens Energy and Automation, Inc. Analytical Instrumentation; 1996.
- [25] SHELXTL reference manual, version 5.03. Madison, Wisconsin, USA: Siemens Energy & Automation, Inc., Analytical Instrumentation; 1996.
- [26] Tarbin JA, Barnes KA, Bygrave J, Farrington WH. Analyst 1998;123:2567-71.
   [27] Garbisch Jr EW. Conformations. VI. Vinyl-allylic proton spin couplings. J Am Chem Soc 1964:86:5561-4.
- [28] Gabbutt CDB, Mark Heron BM, Kilner C, Kolla SB. Org Biomol Chem 2010;8: 4874–83.
- [29] Le Goff T, Wood S. Production of malachite green oxalate and leucomalachite green reference materials certified for purity. Anal Bioanal Chem 2008;391: 2035–45.