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Self-Assembled Superstructure of Xanthene Derivatives

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Abstract Various multi carbon homologations of 9phenyl-9H-xanthen-9-ol (1) were obtained through a C-C bond formation by reacting it with various enolisable ketones in the presence of 1,1'-(ethane-1,2-diyl)dipyridinium bistribromide (EDPBT). All the ten derivatives along with the starting xanthen-9-ol have been characterized by single crystal X-ray diffraction. They all form self-assembled superstructure in the solid state. The self-assembling patterns in these supramolecular architectures were explained based on steric and electronic nature of the pendant arm.

Keywords Supramolecular · Self-assembly · Hydrogenbonding · Superstructure · Xanthene derivatives

Introduction

Intermolecular interactions play a central role in supramolecular chemistry, materials science and biology. Their understanding has allowed, for instance, crystal engineering to evolve and some new related concepts as tecton and synthon are now of common use in the field [1]. Intermolecular interactions enable us to put molecules into desired positions to create novel functional nanostructures which have received great attention because of their potential applications ranging from electronics to medicine [2]. The energy range for hydrogen-bond as well as its directionality

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facilitates the making of highly organized assemblies so that molecular species with functional groups suitable for hydrogen-bond formation constitute a target class of compounds for supramolecular aggregates [2]. A current topic of hydrogen bond research is directional interactions of the types C-H···Y [3] and X-H··· π [4]. In crystal structures, these types of weak hydrogen bonds are often found interconnected with 'normal' or other weak hydrogen bonds, forming motifs that are topologically analogous with conventional hydrogen bond patterns. Several authors have taken this as a manifestation of cooperativity phenomena [5]. A set of weaker hydrogen bonding interactions has also been recognized to play an important role in protein structure and stability [6]. This set includes N- $H\cdots\pi$, O-H $\cdots\pi$, C-H \cdots O and C-H $\cdots\pi$. The overall stabilization energy of these interactions is much smaller (not more than a few Kcal/mol), but is still significant. These weak interactions are suggested to constitute one of the important factors in controlling the crystal packing of molecules [7].

Xanthene derivatives are useful pharmaceuticals such as, muscarinic receptor antagonist, [8] cancer chemotherapy, [9] trypanothione reductase inhibitor, [10] and nonpeptidic inhibitors, [11] as mGluR1 enhancer [12]. They are also useful as dyes, [13] photosensitisers, [14] as ligand for asymmetric catalysis [15]. Xanthene derivatives have the propensity to form inclusion compounds with various aromatic compounds [16].

Here we report the programmed design of few xanthenol derivatives. Various multi carbon homologations **1a–1j** of 9-phenyl-9H-xanthen-9-ol (**1**) were obtained through a C–C bond formation [17]. The attack to xanthenyl carbocation is from the thermodynamically stable enolizable side of the unsymmetrical ketones. Due to a complete shift in the equilibrium in favour of more stable enolizable ketone

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which has large steric factor, no reaction was observed during the addition of 3-methyl-butan-2-one to alcohol 1. We were interested in the self-assembled superstructure in solid state of 9-phenyl-9H-xanthen-9-ol (1) and change of supramolecular architect with variation of the side arm of the xanthene derivatives **1a–1j**.



Experimental

All the chemicals were obtained from Sigma-Aldrich Chemical Co. and used as obtained. Intensity data of the single crystals were collected with Bruker Smart Apex-II CCD diffractometer using graphite monochromated MoKa radiation ($\lambda = 0.71073$ Å) at 298 K. Cell parameters were retrieved using SMART [18] software and refined with SAINT [18] on all observed reflections. Data reduction was performed with the SAINT software and corrected for Lorentz and polarization effects. Absorption corrections were applied with the program SADABS [19]. The structure was solved by direct methods implemented in SHELX-97 [20] program and refined by full-matrix leastsquares methods on F². All non-hydrogen atomic positions were located in difference Fourier maps and refined anisotropically. The hydrogen atoms were placed in their geometrically generated positions. All the colourless crystals were isolated from ethyl acetate and hexane mixture (8:2) at room temperature. All the data collections were done at room temperature. The important crystallographic parameters of the reported compounds are given in Table 1 and 2.

Results and discussion

In order to delineate our objectives of supramolecular selfassembly, we have carried single crystal X-ray diffraction studies of all the xanthenol derivatives **1a–1j** along with its starting compound **1**. Critical investigation of the solid state structure can help us to reveal the effect of variation of alkyl and aryl appendage on the supramolecular assembly/crystal engineering. Here we present a combined structural study of the 10 xanthene derivatives **1a–1j** along with its starting compound **1**. They form different solid state structure of interconnected conventional and non-conventional hydrogen bonds.

The ORTEP [21] diagram of 1 with atomic numbering scheme is shown in Fig. 1. In the asymmetric unit two molecules of 1 crystallizes in the opposite directions. Compound 1 structure is refined in non-centrosymmetric space group P1. We have tried to refine the structure of 1 in centrosymmetric space group P-1. However, the refinement does not behave properly. Phenyl ring is oriented in an almost perpendicular direction with respect to the xanthene ring systems. Oxygen atoms of alcohol groups participates in the formation of dimeric unit via the formation of intermolecular strong O–H···· π hydrogen bonding network. Each of these dimeric units are interconnected to the neighboring dimeric units via the formation of C-H $\cdots\pi$ type of hydrogen bonding (Fig. 2). Combination of various types of intermolecular hydrogen bonding network results in the formation of 3D pillared staircase organic network structure (Fig. 3). The distance between two parallel staircases is 3.959 Å, while distance between each stair is 7.628 Å. The rectangular boxes of dimensions 8.161 Å \times 5.337 Å, formed by the two oppositely oriented molecules in the asymmetric unit constitute the pillar of the staircase.

The ORTEP diagram of 1a with atomic numbering scheme is shown in Fig. 4. In 1a also the asymmetric unit consists of two molecules like its starting compound 1. But unlike compound 1 it shows the presence of C-H····O type hydrogen bonding network instead of strong O-H···· π type hydrogen bonding to form the dimeric unit, due to the absence of alcoholic hydrogen. Oxygen atoms of xanthene unit participate in intermolecular hydrogen bonding network, unlike compound 1. C-H....O type hydrogen bonding forms the linear array along crystallographic a axis. The C-H····O type hydrogen bonding in parallel linear array is pointed in the opposite directions (Fig. 5). Each of these linear arrays are connected to the neighboring oppositely directed arrays through the formation of C-H···· π type of hydrogen bonding. Overall hydrogen bonding network results in the formation of 3D alternate continuous wave-like tape and discrete box network (Fig. 6). One of the two molecules in the asymmetric unit forms the box of dimension 6.580 Å \times 5.887 Å.

The ORTEP diagram of **1b** with atomic numbering scheme is shown in Fig. 7. In **1b** the asymmetric unit consists of one molecule unlike **1a**, due to the presence of extra bulky benzene ring in the pendant arm. Two phenyl rings are almost perpendicular and oriented in the

	Table 1	Crystallographic	data for t	the compounds	1-1e
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	1	1a	1b	1c	1d	1e
Empirical formula	$C_{19}H_{14}O_2$	$C_{22}H_{18}O_2$	$C_{27}H_{20}O_2$	$C_{25}H_{22}O_2$	C ₂₄ H ₂₀ O ₂	C ₃₄ H ₂₆ O ₂
CCDC No.	288546	288549	288547	607501	607503	607502
Fw	274.30	314.36	376.43	354.43	340.40	466.55
Temp, K	298(2)	298(2)	298(2)	298(2)	298(2)	298(2)
Radiation	Mo Ksα	Μο Κα	Μο Κα	Μο Κα	Μο Κα	Μο Κα
Wavelength	0.71073 Å	0.71073 Å				
Crystal system	triclinic	orthorhombic	monoclinic	orthorhombic	monoclinic	orthorhombic
Space group	P1	P2(1)2(1)2(1)	P2(1)/n	P2(1)2(1)2(1)	P2(1)/c	Pbca
a, Å	8.7116 (3)	9.9339 (14)	8.9261(11)	8.7476(19)	13.6932(10)	22.6969(6)
b, Å	8.9282 (4)	14.1874 (19)	21.850(3)	9.924(2)	10.0550(7)	9.6153(2)
c, Å	10.3514 (4)	23.786 (3)	10.8533(14)	21.511(5)	12.8131(10)	23.1193(6)
α, deg	81.577(3)	90.00	90.00	90.00	90.00	90.00
β , deg	71.429 (3)	90.00	111.747(2)	90.00	100.296(4)	90.00
γ, deg	66.610 (2)	90.00	90.00	90.00	90.00	90.00
V, Å ³	700.30(5)	3352.4(8)	1966.2(4)	1867.4(7)	1735.8(2)	5045.5(2)
Z	2	8	4	4	4	8
μ	0.083	0.079	0.079	0.078	0.081	0.073
F(000)	288	1328	792	752	720	2060
GOF(S)	1.415	1.061	3.062	0.991	1.029	0.963
final R indices	R1 = 0.0389	R1 = 0.0386	R1 = 0.0430	R1 = 0.0481	R1 = 0.0424	R1 = 0.0758
$[\mathrm{I}>2\sigma~(\mathrm{I})]$	wR2 = 0.1027	wR2 = 0.0852	wR2 = 0.0651	wR2 = 0.0829	wR2 = 0.1022	wR2 = 0.1448
R indices (all data)	R1 = 0.0538	R1 = 0.0502	R1 = 0.0560	R1 = 0.0865	R1 = 0.0558	R1 = 0.2498
	wR2 = 0.1135	wR2 = 0.0921	wR2 = 0.0665	wR2 = 0.0952	wR2 = 0.1108	wR2 = 0.2109

opposite directions with respect to the xanthene ring. Each molecule forms staircase type intermolecular C-H···· π type hydrogen bonding and each staircase is interconnected via C-H····O type hydrogen bonding through the oxygen atom of the carbonyl group in the side arm, while xanthene ring oxygen does not take part in this hydrogen bonding network like compound **1** (Fig. 8). Overall results in these extensive hydrogen bonding network is 3D zig-zag tape structure (Fig. 9) along crystallographic *a* axis. Adjacent zig-zag tapes are oriented in the opposite directions.

Cyclic aliphatic ketones such as cyclohexanone and cyclopentanone gave the corresponding addition product **1c** and **1d**. Incidentally, there is a striking similarity between the structural arrangements of cyclohexanone (**1c**) and cyclopentanone (**1d**) addition products. For instance, both of the compound **1c** and **1d** has similar solid-state structural disposition (Fig. 10) in space. Pendant phenyl ring and the cyclic ketone units are disposed in the opposite direction with respect to the xanthene unit. Pendant phenyl ring and the cyclic ketone make an angle of 112.12° and 114.26° respectively with xanthene core. **1c** form zig-zag linear array along *a* axis via C–H…O type hydrogen bonding (C15–H15…O1 = 2.605 Å) and the adjacent linear arrays are oriented in the opposite direction (Fig. 11a).

An internal comparison of the packing patterns of **1c** and **1d** reveals certain interesting features, for instance, whereas the compound **1c** forms only C–H···O type hydrogen bonding while **1d** shows the presence of C–H···O, C–H···· π and π – π type interactions (Fig. 11b). Unlike **1c**, in compound **1d** both the oxygen atoms form C– H···O hydrogen bonding (C1–H1···O1 = 2.664 Å and C19–H19···O2 = 2.671 Å). Weaker C–H···· π interactions are also responsible for the formation of organic network (C5–H5··· π (C14–C19) = 3.378 Å and C24–H24a··· π (C1– C6) = 3.234 Å). It also shows the presence of π – π interactions (π (C14-C19) ··· π (C14–C19) = 4.691 Å). It forms mosaic structural motif.

Other symmetrical ketone, 1,3-diphenyl-propane-2-one gave the expected product **1e** (Fig. 12). In compound **1e** one of the pendant phenyl ring (C25–C30) is almost perpendicular to the xanthene unit while the other phenyl rings (C11–C16) is almost parallel to the xanthene unit (Fig. 12). Similar to that of **1c** and **1d**, here also the solid-state structure is mainly governed by the setric factor rather than the hydrogen bonding interactions. Interestingly it forms both inter and intra-molecular C–H···· π type interactions (*inter* C24–H24··· π (C1–C32) = 2.997 Å and *intra* C18–H18b··· π (C11–C16) = 3.422 Å). It forms ladder like 3D organic network (Fig. 13).

	1f	1g	1h	1i	1j
Empirical formula	$C_{23}H_{20}O_2$	$C_{25}H_{24}O_2$	$C_{24} H_{22} O_4$	$C_{28} H_{22} O_2$	C ₅₀ H ₄₄ O ₈
CCDC No.	288548	288545	607505	607504	607500
Fw	328.39	356.44	374.42	390.46	772.85
Temp, K	298(2)	298(2)	298(2)	298(2)	298(2)
Radiation	Μο Κα	Μο Κα	Μο Κα	Μο Κα	Μο Κα
Wavelength	0.71073 Å	0.71073 Å	0.71073 Å	0.71073 Å	0.71073 Å
crystal system	orthorhombic	orthorhombic	orthorhombic	monoclinic	monoclinic
Space group	P2(1)2(1)2(1)	Pbca	P2(1)2(1)2(1)	P2(1)/n	P2(1)/c
a, Å	9.4523 (2)	10.5359 (3)	9.7748(2)	9.7125(5)	22.8334(8)
b, Å	11.6668 (3)	18.7269 (6)	10.7497(2)	13.4710(7)	9.7959(4)
c, Å	16.0143 (4)	19.5093 (7)	19.0446(3)	16.0757(8)	18.5098(6)
α, deg	90.00	90.00	90.00	90.00	90.00
β , deg	90.00	90.00	90.00	96.890(3)	102.171(2)
γ, deg	90.00	90.00	90.00	90.00	90.00
V, Å ³	1766.03(7)	3849.3(2)	2001.13(6)	2088.11(18)	4047.1(3)
Z	4	8	4	4	4
μ	0.077	0.076	0.081	0.077	0.085
F(000)	696	1520	728	824	1632
GOF(S)	1.847	2.730	1.056	0.991	0.992
final R indices	R1 = 0.0381	R1 = 0.0612	R1 = 0.0465	R1 = 0.0602	R1 = 0.0565
$[\mathrm{I}>2\sigma(\mathrm{I})]$	wR2 = 0.0498	wR2 = 0.0739	wR2 = 0.1024	wR2 = 0.1158	wR2 = 0.1198
R indices (all data)	R1 = 0.0623	R1 = 0.0959	R1 = 0.0814	R1 = 0.1990	R1 = 0.1162
	wR2 = 0.0515	wR2 = 0.0758	wR2 = 0.1175	wR2 = 0.1627	wR2 = 0.1437

Table 2 Crystallographic data for the compounds 1f-1j



Fig. 1 ORTEP view of 1



However, when a similar reaction was performed with an unsymmetrical ketone such as butan-2-one, the sole product 3-(9-phenyl-9H-xanthen-9-yl)-butan-2-one (**1f**) obtained. (Fig. 14). In spite of the steric hindrance, the regioselectivity of the product is governed by the formation of stable enolate, giving **1f** exclusively. However, unsymmetrical and one side sterically hindered ketone,

Fig. 2 O–H···· π and C–H···· π H-bond in 1 along *c*-axis

4-methyl-pent-2-one gave the product 4-methyl-1-(9phenyl-9H-xanthen-9-yl)-penta-2-one (**1g**) through a kinetically controlled enolate. This is in spite of the fact that even though enolization is expected to favor towards a thermodynamically stable form but a large steric factor



Fig. 3 3D pillared staircase organic network structure in 1



Fig. 4 An ORTEP view of 1a



Fig. 5 Formation C–H····O and C–H···· π hydrogen bonding network in **1a** along *c* axis

due to the adjacent isopropyl group (Fig. 14), the attack is only possible from the less hindered enolizable side. Unlike **1e**, oxygen atom of the carbonyl group in the side arm of **1f** participate in C–H····O type hydrogen bonding network like **1b**. Each carbonyl oxygen atom forms three C–H····O type hydrogen bonds. Two of them form stable sixmembered hydrogen bonded ring, which help to form



Fig. 6 Alternate box and wave-like tape structure in the compound **1a** along *a* axis



Fig. 7 An ORTEP view of 1b



Fig. 8 C–H····O and C–H···· π hydrogen bonding network in 1b

infinite 2D tape structure along *a* axis. Third C–H····O type hydrogen bond forms with adjacent aromatic hydrogen of xanthene unit, with alternate up and down direction with this 2D tape structure. Overall hydrogen bonding results wave like tape structure along crystallographic *c* axis (Fig. 15). In **1g** only the pendant carbonyl oxygen atom forms C–H····O type hydrogen bonding which form 1D



Fig. 9 Zig-zag tape structure in the compound 1b along a axis



Fig. 10 An ORTEP view with atom numbering scheme of 1c and 1d

linear network along crystallographic c axis. Each T-shaped molecule assembled in the crystal as a 3D zig-zag tape structure (Fig. 15).



Fig. 11 Packing of (a) 1c and (b) 1d



Fig. 12 An ORTEP view of 1e

Neither of the above observations has however been manifested during the reaction of 3-methyl-butane-2-one with 1 under an identical condition. Analysis of product



Fig. 13 Packing diagram of 1e along a



Fig. 14 An ORTEP view of 1f and 1g

showed an oxygen-inserted product from the more hindered side of the enolized ketone giving the oxygen inserted product **1h** as shown (Fig. 16). This can be explained only if the reaction goes via a radical mechanism. No signal for radical could be detected when reaction



Fig. 15 Packing diagram of 1f and 1g



Fig. 16 An ORTEP view of 1h

was monitored by EPR. It was found that formation of product **1h** was due to the contamination of corresponding hydroperoxide obtained by a radical autooxidation at the tertiary carbon. When reaction was performed with a freshly distilled ketone under a nitrogen atmosphere, no reaction occurred even after 3 days. In compound **1h**, both the carbonyl oxygen atom as well as the xanthene oxygen atom form C–H····O type hydrogen bonding (C4–H4···O1 = 2.556 Å and C17–H17···O2 = 2.526 Å). Similar to that of compound **1e**, compound **1h** also form relatively stronger intra-molecular C–H···· π type interactions (C23–H23C··· π (C6-C10) = 2.919 Å). Peroxide oxygen atoms do not participate in any such type of



Fig. 17 Packing diagram of 1h



Fig. 18 An ORTEP view of 1i and 1j

interactions. Overall hydrogen bonding results in the formation of brick wall network along a axis (Fig. 17).

Two other unsymmetrical ketones *viz.* 1-phenyl-propan-2-one and ethyl acetoacetate were reacted with **1**, giving product **1i** and **1j** respectively. The regiochemistry of the product corresponding to the attack by the thermodynamically stable enolate. The ORTEP diagram with atom numbering scheme of compound **1i**, and **1j** is shown in Fig. 18. Similar to the starting compound **1** and **1a**, compound **1j** the ethylacetoacetate adduct also crystallizes with two molecules in the asymmetric unit. Similar to that of **1e**,



Fig. 19 Packing diagram of 1i

compound **1i** also possess only C–H···· π type interactions, but only inter-molecular interactions (C23–H23··· π (C2-C7) = 3.227 Å). In solid state, it packs as flower like mosaic structure in 3D (Fig. 19). Similar to the starting compound 1, compound 1j also crystallizes with two molecules in the asymmetric unit (Fig. 18). Similar to the compound 1h, compound 1j also shows the presence of C-H···O and C-H···· π type of interactions. Unlike **1g**, in compound 1j both the oxygen atoms form C-H···O hydrogen bonding (C10-H10...O6 = 2.536 Å, C17-H17...O3 = 2.563 Å, C46-H46...O1 = 2.548 Å and C51-H51a···O6 = 2.689 Å). Weaker C–H···· π interactions are also responsible for the formation of organic network $(C40-H40c\cdots\pi (C43-C48) = 2.964 \text{ Å})$. Two symmetrically independent molecules in the unit cell form snow flake mosaic structure (Fig. 20).

In conclusion, the design strategy used in this work has successfully used to have wide range of xanthene



Fig. 20 Packing diagram of 1j

derivatives. These compounds form variety of superstructure in the solid state via formation of different types of weak interactions. Variation in the side arm of the xanthene derivatives results in the formation of different types of self-assembled superstructure. Their self-assembling pattern was explained based on their steric and electronic nature. It is also clear that the design strategy should be more widely applicable to investigate these xanthene derivatives as a supramolecular synthons in crystal engineering, which is currently going on in our laboratory.

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