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Four component domino reaction for the synthesis of highly functionalized dimeric tetracyclic dilactam fluorophores: H-bond aided self-assembly†

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G. Ramachandran,^{ab} A. Raman,^{cd} S. Easwaramoorthi,^{cd} R. S. Rathore^e
and K. Sathiyarayanan^{*a}

A series of new dimeric tetracyclic dilactam fluorophores (DTDF) consisting of diazabicyclooctane-dione (DBOD) fused to tetrahydronaphthalene (THP) was designed and synthesized from a simple precursor. The monomers showed enhanced emission in THF–water solvent and also benzene-dimer like absorption and fluorescence, originating from the hydrogen-bonding aided self-assembly of dilactams. The crystal structures revealed water-mediated molecular aggregates with several hydrogen-bond bridges formed by water.

In both chemistry and biology, the hydrogen bond plays an essential role, typically characterized by a relatively weak interaction involving an electronegative proton acceptor, a hydrogen atom, and an electronegative proton donor.^{1–5} Several theoretical studies have been conducted at diverse levels of calculation to study the blue-emitting fluorophore, possessing hydrogen bonds in OLEDs.^{6–10} Dykstra *et al.*^{11–13} hypothesize that the shifts in vibrational frequency of the hydrogen bonds are based on the monomer properties such as polarizability and the electrical moments. Over the past few decades of research in organic materials, significant importance has been devoted to the design and synthesis of molecules possessing hydrogen-bonded as well as π -conjugated molecules with specific properties.^{14–16} Thus, highly emissive organic fluorescent materials are of significant interest to and develop a new class of AIE chromophores. Benzene dimer association with π – π interactions between the aromatic rings has been a widely explored

area of AIE chromophores,^{17–21} whereas self-assembled bridged lactams, possessing intermolecular hydrogen bonding along with the water interaction between the molecules have not been reported so far. The options for mounting both in one reaction are extremely limited; however, this interaction was introduced successfully into organic molecules by employing an efficient method to synthesize dimeric tetracyclic dilactams. Numerous methods have been developed to study the AIE effect in organic materials, but still, it remains challenging. The aggregated species showed π – π stacking between the benzene rings to form the benzene dimer, and an intermolecular interaction between the lactam amides and also between the water molecules with lactam amides. To the best of our knowledge, such interactions between the lactam amides and water molecules exhibiting the AIE effect have not been reported so far. For the first time, we designed and synthesized highly functionalized DTDF, possessing four stereogenic centers from simple starting materials: α -tetralone, aryl aldehyde, and cyanoacetamide.^{21,22} The molecular aggregates are characterized by quinoline dimers linked through dimeric N–H...O hydrogen bonds. An examination of the crystal structure clearly showed that these molecules consist of fused bridged dilactam and show fluorescence behaviour due to the formation of aggregation in the crystal packing.²³ Another interesting phenomenon for the formation of aggregation in these systems is the water hydrogen bonding between the molecules.

As an initial test to study the reaction conditions, we investigated the efficiency of the catalyst for this reaction under various conditions to determine the optimum conditions. In this model reaction, several metal hydroxides were screened to optimize the reaction conditions. From Table S1† (entry 1–9), it can be seen that the reaction proceeded only in the presence of metal hydroxides and formed highly functionalized benzo[h]quinoline. The solvent effect was the next factor considered for better yield. Thus, experiments were carried out in various solvents, such as polar protic, aprotic and nonpolar solvents using 0.5 mol% NaOH as the catalyst for all the reactions. From Table S1,† it can be seen that the optimal condition for these reaction transformations was 0.5 mol% NaOH in methanol.

^aChemistry Division, School of Advanced Sciences, VIT University, Vellore, India.
E-mail: sathiya_kuna@hotmail.com; Fax: +91 4162243092

^bDepartment of Chemical Sciences, Indian Institute of Science Education and Research (IISER) Mohali, S A S Nagar Manawali PO, Punjab – 140306, India

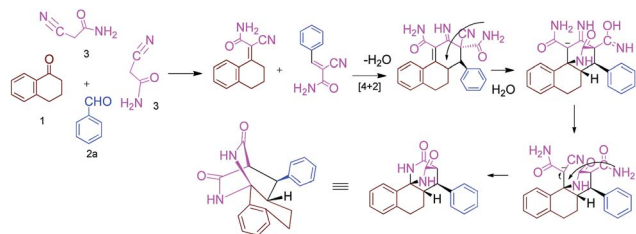
^cChemical Laboratory, CSIR-Central Leather Research Institute, Adyar, Chennai – 600020, India

^dAcademy of Scientific and Innovative Research (AcSIR), Anusandhan Bhawan, 2 Rafi Marg, New Delhi – 110001, India

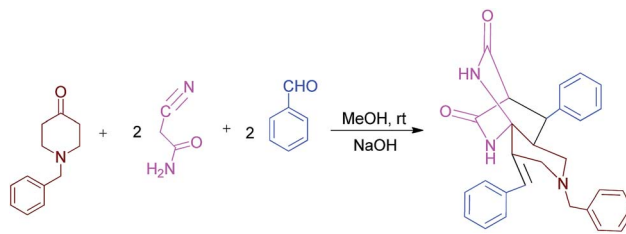
^eBioinformatics Infrastructure Facility, School of life sciences, University of Hyderabad, Hyderabad – 500046, India

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Communication



Scheme 1 A proposed mechanism for the formation of tetracyclic dilactams.



Scheme 2 Synthesis of highly functionalized triazatricyclo [6.2.2.0^{1,6}] dodecane-9,12-dione.

We then applied these conditions to synthesize a series of substituted DTDFs. The synthesized DTDF possessed four stereogenic centers, in which two quaternary amine functionalities were obtained. Such an observation is certainly rare, fascinating and quite interesting in organic chemistry.²¹

The proposed mechanism for the formation of this domino reaction is shown in Scheme 1. The two different Knoevenagel condensations with cyanoacetamide using α -tetralone and benzaldehyde give two intermediates, which in turn rearrange to form a C–C bond, followed by a [4 + 2] cycloaddition and an intramolecular Michael-type addition. We also examined the scope and limitations of these four component domino reactions (Table 1). When the reaction was carried out with another cyclic ketone as a substrate instead of α -tetralone, the reaction proceeded along a different path. The behaviour of phenylacrylamide fluorophore and the reaction with the other cyclic ketone was studied in our laboratories. Further, when the equivalence level of cyanoacetamide in the reaction was reduced to 1 eq. from 2 eq., the reaction proceeded in a different manner. Similarly, we also tried these reactions with aliphatic aldehydes instead of aryl aldehydes under the same conditions but failed to achieve the desired product.

Initially, we carried out this reaction using similar conditions by using another cyclic ketone to obtain tricyclo dilactam fluorophore, but unexpectedly we obtained a non-fluorescence

compound of highly functionalized triazatricyclo [6.2.2.0^{1,6}] dodecane-9,12-dione. In order to investigate this further, we focused on the mechanisms involved, in order to study the path in which the reaction proceeded. These results suggested that the mechanism followed an aldol reaction/condensation/cyclisation path, followed by dehydration to give the desired product (Scheme 2).

UV-visible absorption and fluorescence spectral (Fig. 1) studies for these compounds were carried out to understand the electronic properties and also to explore the influence of the electron-donating or -withdrawing nature of the substituent on the electronic properties. The representative absorption spectra of **4h** measured in tetrahydrofuran (THF) solvent showed peaks at 255, 336, 348, 396, and 412 nm, which suggests that it exhibits a concentration-dependent behaviour. The lowest energy absorptions disappeared when the concentration of the sample was maintained in the micromolar range.

The observed concentration-dependent behaviour could have originated from the dimer or from the aggregates of **4h**. Indeed, the electron-withdrawing or -donating nature of the substituent had only a subtle effect on the absorption spectrum. Notably, the chromophoric unit of these molecules was restricted to the benzene moiety alone, and the remaining non-conjugated skeleton did not influence the electronic properties to a significant extent (Table S2†). Furthermore, the electronic

Table 1 Domino reaction for the synthesis of multifunctionalized tetracyclic dilactams^a

Entry	ArCHO	Product	Yield ^b (%)	Entry	ArCHO	Product	Yield ^b (%)
1	H	4a	58	7	4-F	4g	80
2	2-CF ₃	4b	62	8	2-Me	4h	83
3	2-Br	4c	69	9	4-Me	4i	80
4	4-OMe	4d	45	10	2-Cl	4j	75
5	2-F	4e	89	11	4-Cl	4k	89
6	3-F	4f	65	12	1-Naphthaldehyde	4l	95

^a Reaction conditions: α -tetralone (10 mmol); benzaldehyde (10 mmol) and cyanoacetamide (20 mmol) at room temperature (30 °C). ^b Isolated yield.

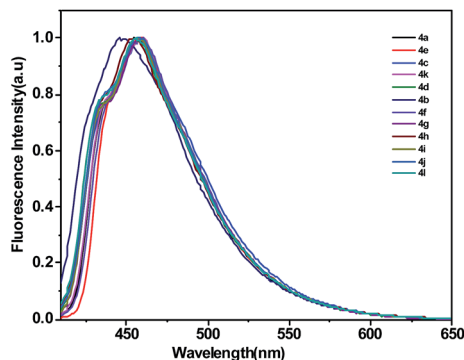


Fig. 1 Emission spectra for the synthesized compound 4a–4l.

absorption spectrum of benzene was generally observed in the range of 300 nm. The significantly red-shifted absorption spectrum of tetracyclic dilactams is quite intriguing.

To further understand the electronic properties, we calculated the molecular orbital at the B3LYP/6-31G level using a Gaussian 03 programme.²⁴ Initially the geometry of the tetracyclic dilactams was optimized at the B3LYP/6-31G level using the single crystal X-ray structure as the input file. It was observed that the band gap between the highest occupied molecular orbital (HOMO) to the lowest unoccupied molecular orbital (LUMO) corresponded to 5.72 eV in the gas phase, a value corresponding to the transition from the ground to the excited state of monomeric benzene.¹⁸ Hence, the transitions in the lower energy region may have been due to the dimeric or aggregated tetracyclic dilactams, aided by the intermolecular hydrogen bonding interactions.

It has been known, particularly, for benzene-based systems, that the dimer or higher aggregates absorb at longer wavelengths than that of monomers. Nevertheless, transannular interactions between the benzene ring in cyclophane analogous systems lead to a longer wavelength absorption peak, which was observed below 300 nm.¹⁹ However, **4a** showed the longest absorption spectrum close to 400 nm. To the best of our knowledge, this is the first observation with benzene aggregates, showing the least energy absorption in the visible region. The fluorescence spectra of **4a** in THF solvent showed maximum emission wavelengths at 426 and 448 nm, respectively, with a mirror image relationship with the lowest energy absorption spectrum. The compound **4l**, naphtho[h]quinoline-2,12(3H)-dione also showed concentration-dependent absorption.

At higher concentrations, the ground state dimer absorption was predominant at 265, 336, 346, 378, 394 and 414 nm, while monomer spectra were noticed at lower concentrations. The observed spectra matched with the reported value for the dimer absorption where naphthalene moieties were covalently tethered to the dendrimer moiety.²⁰ Indeed, intense fluorescence at 438 and 459 nm, was observed for naphthalene dimers in THF solutions and that of monomer was observed at 328, 340 nm along with the shoulder at 354 nm (Fig. 2). The red-shifted absorption and emission spectra at higher concentrations occurred solely due to the self-assembly formation, which was aided by the hydrogen bonding interaction.

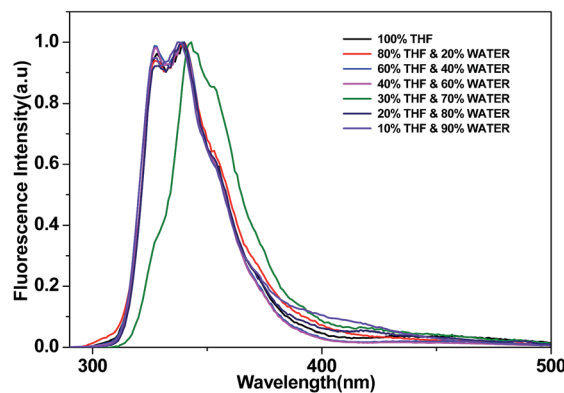
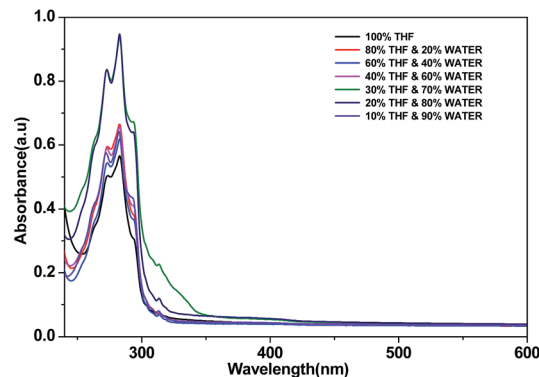


Fig. 2 Absorbance and fluorescence (exi-270 nm) spectrum of compound **4l** in various percentage of water and THF.

To enable the self-assembly even at lower concentrations, we used the reprecipitation method where the concentrated **4l** was rapidly injected into the water and water–THF solvent mixtures in different ratios (v/v). The concentration of **4l** was maintained at 5.42×10^{-6} M, where only monomer absorption was observed. The addition of **4l** to the water–THF mixture caused slight changes in the spectral maxima; however, a significant reduction in the absorbance characteristic of the solvent ratio was noticed. Thus, we inferred that the formed self-assembly was quite stable, as was evident from the lack of time-dependent absorption spectral changes and also due to the absence of precipitation. It should be noted that the solvent aided self-assembled structure formed in the water–THF solvent mixture, at lower concentrations, did not form the naphthalene dimers at higher concentrations (Fig. 3). Nonetheless, the fluorescence from the monomeric units became intense when the water–THF ratio was 20–80%, 40–60%, 60–40%. The dimer also existed in the solid state, as can be understood from the UV-visible diffuse reflectance spectra of the solid samples.

The diffraction quality crystals for **4b** were grown and examined using an X-ray diffraction method.^{25,26,27} The molecular structure is illustrated in Fig. 4. The asymmetric unit comprised 2 conformers (A and B) of **4b** hydrated with three water molecules. In the tetracyclic ring, DBOD and THP were fused together. Moreover, in the reported centrosymmetric structure, the stereogenic centers of DBOD rings (C10 & C11) in **4b** (A) and **4b** (B) assumed R,R configurations. The cyclohexene ring of THP adopted a twisted-chair configuration, while the

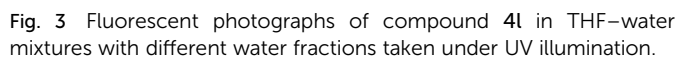


Fig. 3 Fluorescent photographs of compound **4l** in THF–water mixtures with different water fractions taken under UV illumination.

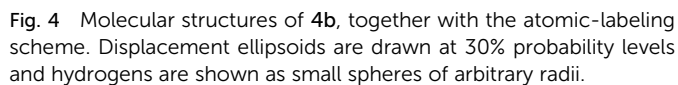


Fig. 4 Molecular structures of **4b**, together with the atomic-labeling scheme. Displacement ellipsoids are drawn at 30% probability levels and hydrogens are shown as small spheres of arbitrary radii.

trifluoromethylbenzene substituent of the DBOD ring was in an equatorial position. Crystal packing of **4b** was characterized by N-H \cdots O-bonded molecular dimers and a water-mediated molecular aggregation. The molecules associated along the *a*-axis to form a channel occupied by water and formed multiple bridge interactions with one of the amide groups in the DBOD bicyclic ring system. These channels at the unit cell corners (see Fig. S3† in the projected unit cell along the *a*-axis) interacted *via* closed dimeric N1A–H1A \cdots O1A interactions between the amide groups of the DBOD ring and were augmented by intermolecular C–H \cdots F interactions (Table S4†).

In summary, we report a novel four-component domino reaction for the synthesis of highly functionalized benzo[h]quinoline-2,12(3H)-dione, which gave access to tetracyclic dilactam. The obtained molecules possessed four stereogenic centers with two quaternary carbon-amino functionalities. All the compounds existed as dimers at higher concentrations, aided by the hydrogen bonding interactions between the amide groups. The dimers showed a higher red-shifted absorption spectrum than the monomers. To the best of our knowledge, this report is the first to specify the interesting finding of tetracyclic dilactam fluorophore, which has an inherently strong effect on the generation of aggregation-induced red-shifted fluorescence properties. In fact, all the compounds showed intense blue fluorescence, with a maximum effect at 460 nm. These molecules can be used as blue emitters. Also, the presence of an amide group may help the use of these molecules as fluorescent markers for probing biological functions.

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- 1 M. L. Huggins, *Science*, 1922, **55**, 459.
- 2 L. Pauling, *J. Am. Chem. Soc.*, 1931, **53**, 1367.
- 3 G. A. Jeffrey, *An Introduction to Hydrogen Bond*, Oxford University Press, New York, 1997.
- 4 G. Desiraju and T. Steiner, *The Weak Hydrogen Bond*, Oxford University Press, New York, 1999.
- 5 L. Xiaosong, L. Lei and H. Bernhard Schlegel, *J. Am. Chem. Soc.*, 2002, **124**, 9639–9647.
- 6 E. Cubero, M. Orozco, P. Hobza and F. J. Luque, *J. Phys. Chem. A*, 1999, **103**, 6394.
- 7 (a) B. J. van der Veken, W. A. Herrebout, R. Szostak, D. N. Shchepkin, Z. Havlas and P. Hobza, *J. Am. Chem. Soc.*, 2001, **123**, 12290; (b) P. Hobza and Z. Havlas, *Chem. Rev.*, 2000, **100**, 4253.
- 8 H. M. Muchall, *J. Phys. Chem. A*, 2001, **105**, 632.
- 9 Y. L. Gu, T. Kar and S. Scheiner, *J. Am. Chem. Soc.*, 1999, **121**, 9411.
- 10 S. Scheiner, T. Kar and Y. L. Gu, *J. Biol. Chem.*, 2001, **276**, 9832.
- 11 S. Liu and C. E. Dykstra, *J. Phys. Chem.*, 1986, **90**, 3097.
- 12 (a) S. Y. Liu, C. E. Dykstra and D. J. Malik, *Chem. Phys. Lett.*, 1986, **130**, 403; (b) S. Y. Liu and C. E. Dykstra, *Chem. Phys. Lett.*, 1987, **136**, 22.
- 13 C. A. Parish and C. E. Dykstra, *J. Phys. Chem.*, 1993, **97**, 9374.
- 14 B. K. An, D. S. Lee, J. S. Lee, Y. S. Park, H. S. Song and S. Y. Park, *J. Am. Chem. Soc.*, 2004, **126**, 10232–10233.
- 15 K. Kokado and Y. Chujo, *J. Org. Chem.*, 2011, **76**, 316–319.
- 16 K. Itami, Y. Ohashi and J. Yoshida, *J. Org. Chem.*, 2005, **70**, 2778–2792.
- 17 K. E. Riley and P. Hobza, *Acc. Chem. Res.*, 2013, **46**, 927–936.
- 18 A. Pentin Yu and L. V. Vilkov, *Physical Methods in Chemistry*, Moscow: Mir., 683, 2003.
- 19 D. J. Cram, N. L. Allinger and H. Steinberg, *J. Am. Chem. Soc.*, 1954, **76**, 6132.
- 20 P. K. Lekha, T. Ghosh and E. Prasad, *Chem. Sci.*, 2011, **123**, 919.
- 21 B. Jiang, S.-J. Tu, P. Kaur, W. Wever and G. Li, *J. Am. Chem. Soc.*, 2009, **131**, 11660–11661.
- 22 B. Jiang, C. Li, F. Shi, S.-J. Tu, P. Kaur, W. Wever and G. Li, *J. Org. Chem.*, 2010, **75**, 2962–2965.
- 23 R. Yoshii, A. Nagai, K. Tanaka and Y. Chujo, *Chem.-Eur. J.*, 2013, **19**, 4506–4512.
- 24 M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery Jr, T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji,

- M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez and J. A. Pople, *Gaussian 03, Revision E.01*, Gaussian, Inc, Wallingford, CT, 2004.
- 25 Bruker, *APEXII (Version 1.08)*, *SAINT-Plus (Version 7.23A)* and *SADABS (Version 2004/1)*, Bruker AXS Inc., Madison, Wisconsin, USA, OR (Oxford Diffraction, 2010), 2004.
- 26 G. M. Sheldrick, *Acta Crystallogr., Sect. A: Found. Crystallogr.*, 2008, **64**, 112–122.
- 27 L. J. Farrugia, *J. Appl. Crystallogr.*, 1997, **30**, 565.