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triimidazo[1,2-a:1',2'-c:1'',2''-e][1,3,5]triazine derivatives
by DFT/NMR integrated approach**

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Chemical shift assignment of mono- and di-bromo triimidazo[1,2-*a*:1',2'-*c*:1'',2''-*e*][1,3,5]triazine derivatives by DFT/NMR integrated approach

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Abstract

Solid state organic compounds, endowed with enhanced emission, have been gaining great attention in the scientific community for their potential application in different areas, such as lighting technologies or bioimaging. In this field, mono- and di-bromo derivatives of triimidazo[1,2-*a*:1',2'-*c*:1'',2''-*e*][1,3,5]triazine have been proposed as new organic molecules presenting a very rich and complex photophysical behavior. Their structures were investigated by standard 1D and 2D NMR experiments, but the correct structural assignment of all proton and carbon resonances was made difficult since the lack of crucial and diagnostic long-range correlations between quaternary carbon and proton signals. Thus, we afforded the correct chemical shift assignment by integrating the experimental data with DFT calculation of NMR parameters. Our findings lay foundation for a structural reference in the organic synthesis and characterization of new congeners of this intriguing class of molecules.

Keywords: NMR, ¹H, ¹³C, DFT, chemical shift, spin-spin coupling constants; aggregation-induced emitters, cyclic triimidazole.

Introduction

The search for new solid state luminogens is a field of ever growing interest due to their potential application in different areas spanning from lighting technologies to bioimaging. However, very frequently, highly emissive molecules result into weakly or even non emissive solid materials due to the notorious phenomenon of aggregation-caused quenching (ACQ). Only recently, compounds characterized by enhanced emission (fluorescence and/or phosphorescence) in the solid state have been reported and classified as aggregation-induced emitters (AIE).^[1,2,3,4,5,6] Among AIE, purely organic materials showing solid state room temperature phosphorescence (RTP) are particularly intriguing with respect to their organometallic counterparts because of their lower toxicity, cost and environmental load. Moreover, specific features potentially associated with organic phosphorescent materials, such as long afterglow lifetimes,^[7,8,9] have opened the way to new possible applications including low-cost anti-counterfeiting technologies, temperature monitoring, sensing and bio-imaging.

Some of us have recently reported on the intriguing photophysical behavior of triimidazo[1,2-*a*:1',2'-*c*:1'',2''-*e*][1,3,5]triazine, **TT**, and its mono- and di-bromo derivatives (**2** and **1** respectively, Figure 1). **TT** is characterized by crystallization induced and mechanochromic emissive behavior, together with room temperature ultralong phosphorescence (RTUP) at ambient conditions (1s) associated with H-aggregation that provides the necessary stabilization of the triplet excitons.^[10]

The presence of one or two heavy (Br) atoms on the **TT** scaffold greatly modifies both its molecular and solid state photophysical behavior. In fact, **1** and **2** are characterized by a very rich and complex photoluminescence with emissions going from molecular fluorescence, dual fluorescence, molecular phosphorescence to supramolecular RTP and RTUP.^[11]

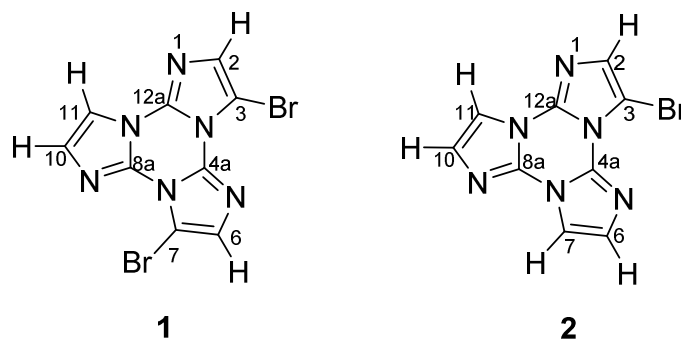


Figure 1. Molecular structures of compounds **1** and **2**.

The structures of **1** and **2** were elucidated by extensive spectroscopic methods including 1D- (^1H and ^{13}C) and 2D NMR experiments (COSY, HSQC, HMBC), as well as single crystal X-ray diffraction and mass spectrometry analysis. Nevertheless, the correct structural assignment of all proton and carbon resonances was made difficult since the lack of crucial and diagnostic long-range correlations between quaternary carbon and proton signals.

In the last years, the application of QM predictions^[12,13] has been gaining a great attention by the scientific community for high accuracy in the reproduction of the experimental NMR properties even at low level of theory^[14,15] and thanks to the increasing computational power. This hybrid approach has been demonstrated a valuable approach for the structural studies of organic compounds, spanning from configurational and conformational assignments^[16,17] and to structure elucidation of natural products.^[18,19] The use of QM-NMR integrated strategy is not limited to stereostructural studies, but could support the total synthesis of natural compounds^[20,21] and also the analysis of ligand-macromolecule interactions.^[22]

In this paper, we address the resonance assignment of **1** and **2** integrating the NMR experimental data with quantum mechanical (QM) calculation of chemical shifts and heteronuclear coupling constants.

Result and Discussion

The analysis of NMR data of **1** led to two hypothesis of chemical shift assignment: **1a** and **1b** (Figure 3). In details, the ^1H NMR spectrum of compound **1**, recorded in $\text{DMSO-}d_6$, showed two singlets (δ_{H} 7.36 and 7.40 ppm) and two doublets (δ_{H} 7.31 and 7.96 ppm, Figure S3,S4). The ^{13}C chemical shifts of their attached carbons could be assigned unambiguously from the HSQC spectrum (Figure S7, Table 4). The ^{13}C NMR spectrum showed 4 CH signals and 5 quaternary carbons peaks (Figure S5). The latter group of signals contains the brominated positions at 95.3 ppm and 95.7 ppm. The structure determination began with an HMBC correlation (Figures 2 and S8) from proton at δ_{H} 7.36 (H-2) to carbon at δ_{C} 95.3 (C-3, ring A). The same proton showed a correlation with a carbon at δ_{C} 136.7 ppm (Figure 2) attributed to the carbon 12a due to its correlation with a signal at δ_{H} 7.31, which belongs to ring C as revealed by the COSY spectrum. Indeed, only a spin system relative to the resonances at 7.31 ppm and 7.96 ppm was observed in the COSY spectrum (see Figure S6 in the Supporting Information). It should be noted that in the HMBC spectrum (Figure 2) is not present a correlation between 7.96 ppm and 136.7 ppm (C-12a).

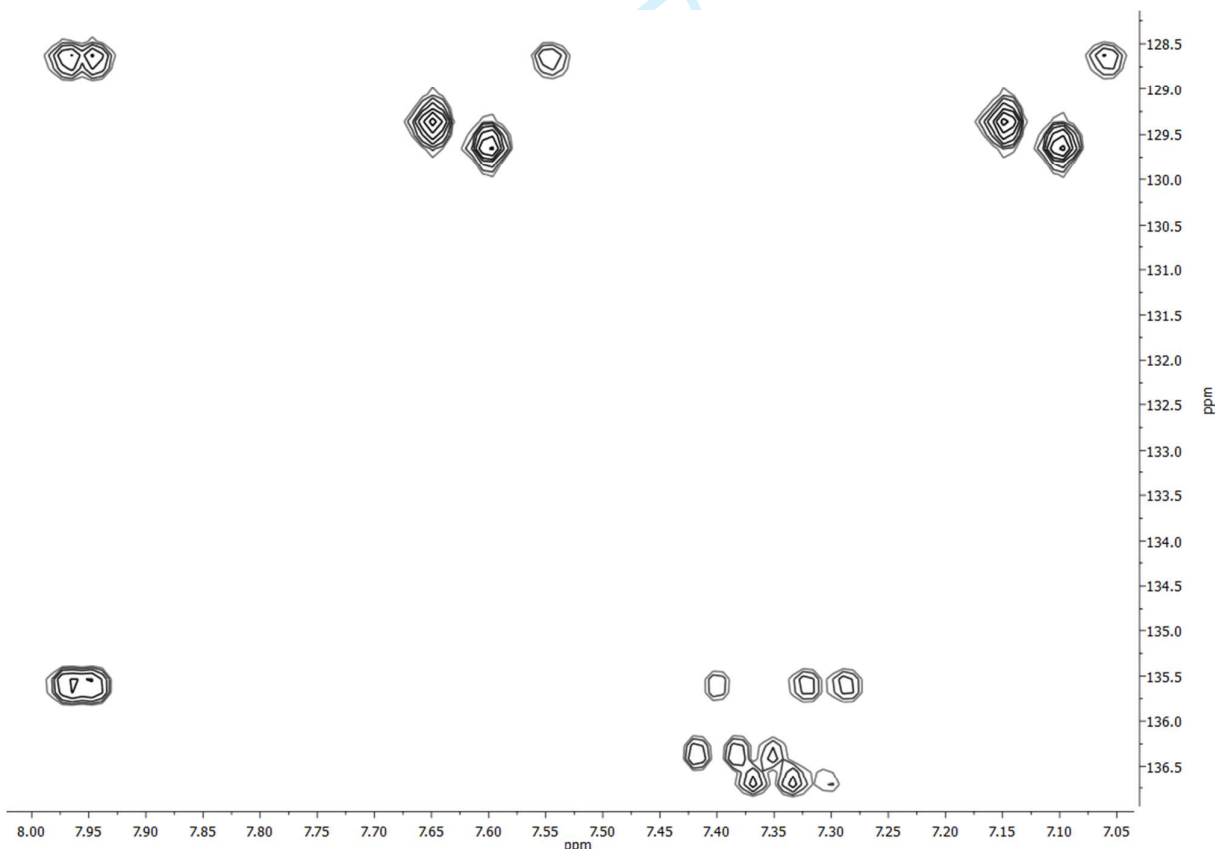


Figure 2. Partial HMBC spectrum of **1**.

Both proton signals H-10 and H-11 showed a long-range correlation with a quaternary carbon at 135.6 ppm, identified as C-8a (Figure 2). Thus, the remaining signal at 7.40 ppm was assigned to H-6. In the HMBC spectrum, the proton H-6 is correlated with carbon at 95.7 ppm (C-7) but also with a carbon at 136.4 ppm attributed to the position C-4a. The H-2 (7.36 ppm) presents a small intensity of correlation peak with C-4a. Another $^4J_{C-H}$ correlation is observed between H-6 and C-8a. The observed heteronuclear correlation of C12a with resonance at 7.31 ppm, and not with 7.96 ppm apparently suggested the assignment **1b** (Figure 3). However, it is noteworthy that the correlation $^3J_{C_{12a}-H_{11}}$ presents an unusual small intensity not comparable with the other observable $^3J_{C-H}$ couplings, such as, C-8a—H-10, C-8a—H-11, C-4a—H-6. Its intensity is comparable with observable $^4J_{C-H}$ couplings: C-8a—H-6 and C-4a—H-2. These considerations could suggest that the heteronuclear coupling between C-12a and H-11 represents a $^4J_{C-H}$ rather than a $^3J_{C-H}$, leading toward the hypothesis **1a** (Figure 3) for the resonance assignment.

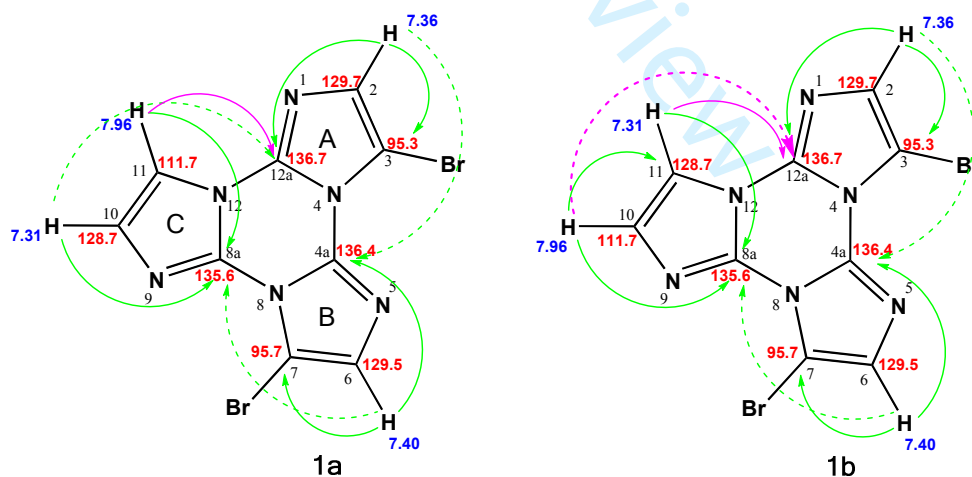


Figure 3. Two hypothetical chemical shift assignments: **1a** and **1b**. The green arrows indicate the observed long range correlations in the HMBC spectrum. The purple arrows refer to the expected heteronuclear couplings. The dashed and continuous lines indicate weak and strong peak intensity, respectively. The 1H and ^{13}C chemical shifts are indicated in blue and red, respectively.

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5 Concerning **2**, the ^1H NMR spectrum (DMSO- d_6 , Figure S9,S10) showed a singlet at δ_{H} 7.37 ppm
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7 and four doublets: δ_{H} 7.27, 7.32, 7.93, 7.99 ppm. The ^{13}C chemical shift of their attached carbons
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9 could be easily assigned from the HSQC spectrum (Figure S13, Table 4). The ^{13}C NMR spectrum
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11 (Figure S11) showed 5 CH signals and 4 quaternary carbon signals. In particular, the resonance at
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13 δ_{H} 95.0 ppm corresponds to the carbon bearing the bromine atom. The COSY coupling networks
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15 led to the identification of two spin systems at: 7.27 ppm and 7.93 ppm, 7.32 ppm and 7.99 ppm
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17 (Figure S12). In the HMBC spectrum (Figures 4 and S14), we observed a correlation from proton at
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19 δ_{H} 7.37 (H-2) to carbon at δ_{C} 95.0 (C-3), (ring A). The same proton showed a correlation with a
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21 carbon at 136.4 ppm allowing the assignment of the carbon 12a (Figure 4). Compared to the
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23 coupling C-12a—H-2, the carbon 12a showed a weaker correlation with a signal at δ_{H} 7.27 ppm.
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25 The C-12a did not show any correlation with proton resonance at 7.93 ppm (Figure 4) that is
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27 coupled to 7.27 as revealed by COSY spectrum, suggesting these two protons as resonances of ring
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29 C (see Figure S12 in the Supporting information). Both proton signals at 7.27 and 7.93 ppm showed
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31 a correlation with a quaternary carbon at 135.7 ppm, identified as C-8a. Similarly to the correlation
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33 of C12a with 7.27 ppm, a very weak coupling was observed between 7.32 ppm and 135.7 ppm. This
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35 carbon did not present a coupling with the proton at 7.99 ppm (Figure 4). These observations were
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37 also made for C12a correlation of ring C proton of **1**.
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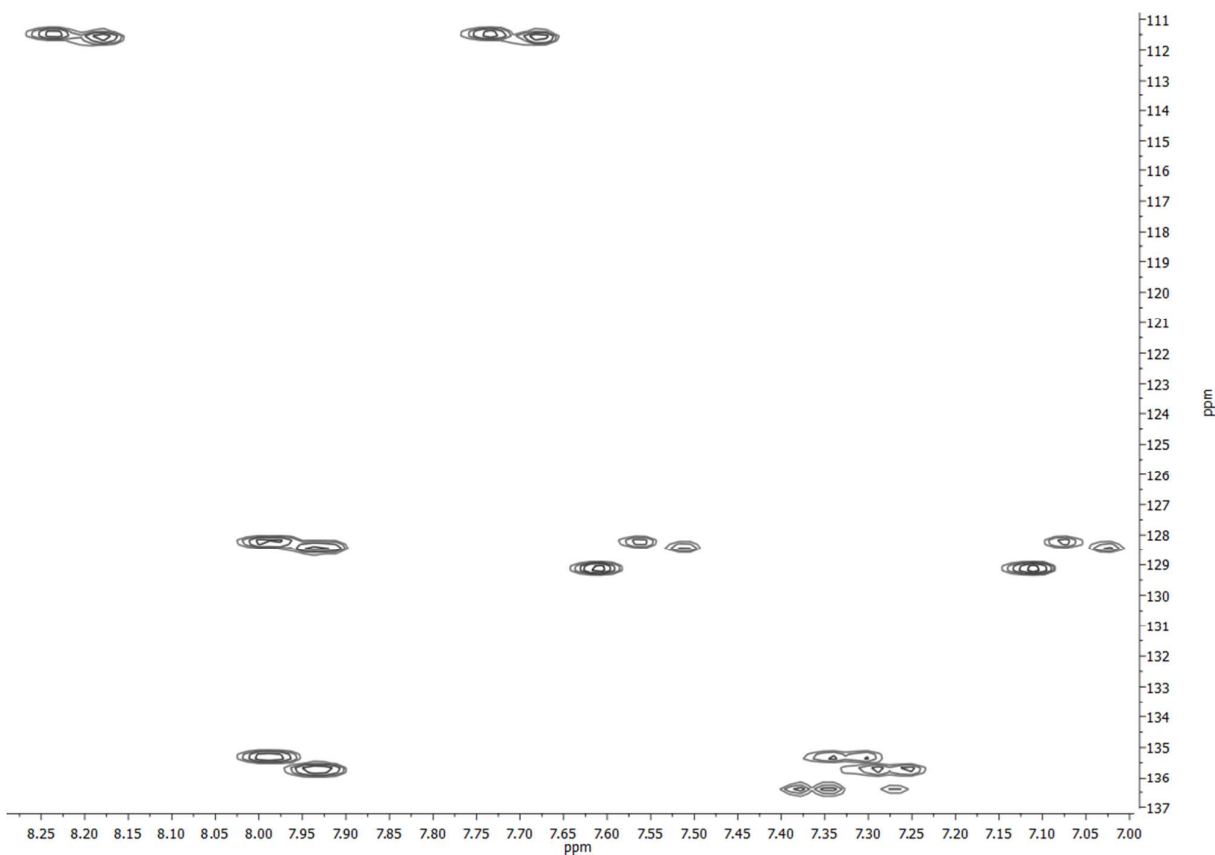


Figure 4. Partial HMBC spectrum of **2**.

The HMBC correlation of both signals at 7.32 ppm and 7.99 ppm with a quaternary carbon at 135.3 ppm allowed to assign the C-4a position. As for **1**, the only observed heteronuclear correlations of C12a with resonance at 7.27 ppm, and C8a with 7.32 ppm could suggest the assignment **2b** (Figure 5). On the contrary, an inspection of peak intensity of HMBC spectrum led to the assignment **2a**.

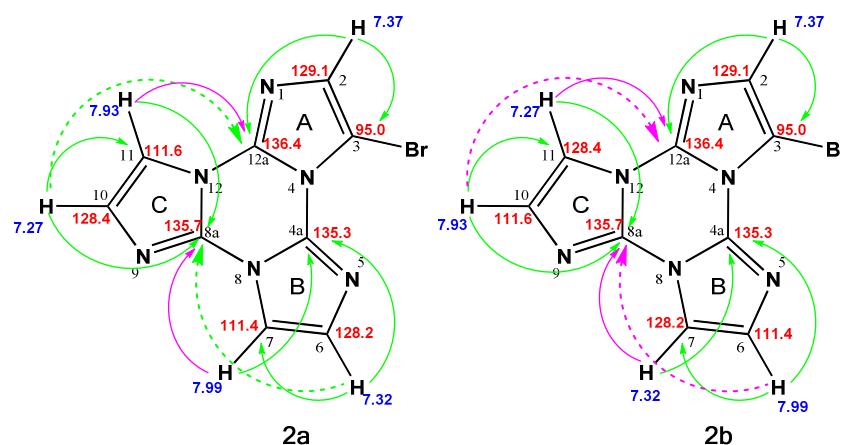


Figure 5. Two hypothetical chemical shift assignments: **2a** and **2b**. The green arrows indicate the observed long range correlations in the HMBC spectrum. The purple arrows refer to the expected heteronuclear couplings. The dashed and continuous lines indicate weak and strong peak intensity, respectively. The ^1H and ^{13}C chemical shifts are indicated in blue and red, respectively.

In order to unambiguously assign all resonances of **1** and **2**, we integrated the experimental data performing quantum mechanical (QM) calculations of ^1H and ^{13}C chemical shifts of two compounds under investigation. In particular, we refined the energies and the geometries by using the DFT level using the MPW1PW91 functional and the 6-31G(d) basis set simulating the presence of dimethylsulphoxide (IEF-PCM). On the so optimized geometries for **1** and **2** the ^1H and ^{13}C chemical shifts were calculated by means of the same functional of the previous step and the 6-31G(d,p) basis set.^[15] The calculated chemical shifts of **1** revealed that the proton H-10 resonates at higher field than H-11 (Table 1). Similarly, the C-10 presented a chemical shifts value lower than C-11 (Table 1). The comparison of the theoretical ^1H and ^{13}C chemical shifts with the two hypothetical assignments (**1a** and **1b**) revealed that the **1a** is in agreement with the predicted values (Table 1). Indeed, the obtained MAE (Mean Absolute Error) values for ^1H and ^{13}C chemical shifts of **1a** are respectively 0.15 and 0.59 ppm against 1.6 and 16.7 ppm for **1b** (Table 1). By analysing the $|\Delta\delta|$ for H-10 and H-11, we find largest errors for the calculated ^1H chemical shifts of **1b** (Table 1). In details, for H-10 and H-11 the $|\Delta\delta|$ are 0.74 and 0.45 ppm against 0.09 and 0.20 ppm of **1a**. The $|\Delta\delta|$ of C-10 and C-11 of **1b** are 18.3 and 15.1 ppm vs. 1.3 and 1.9 ppm of **1a** (Table 1).

Table 1. Comparison of calculated vs. experimental ^1H and ^{13}C NMR chemical shifts of hypothetical assignments **1a** and **1b** in DMSO

position	^1H (ppm)					^{13}C (ppm)				
	1a			1b		1a			1b	
	δ_{calcd}	δ_{exp}	$ \Delta\delta ^{\text{a}}$	δ_{exp}	$ \Delta\delta ^{\text{a}}$	δ_{calcd}	δ_{exp}	$ \Delta\delta ^{\text{a}}$	δ_{exp}	$ \Delta\delta ^{\text{a}}$
10	7.22	7.31	0.09	7.96	0.74	130.0	128.7	1.3	111.7	18.3
11	7.76	7.96	0.20	7.31	0.45	113.6	111.7	1.9	128.7	15.1
MAE^b	0.15		0.59			1.6		16.7		

^a $|\Delta\delta| = |\delta_{\text{exp}} - \delta_{\text{calcd}}|$, absolute differences for experimental versus calculated ^1H and ^{13}C NMR chemical shifts. ^b $\text{MAE} = \Sigma[|\delta_{\text{exp}} - \delta_{\text{calcd}}|]/n$.

The same considerations can be made for compound **2**. The ^1H resonances at H-6 and H-10 are shielded respect to H-7 and H-11 (Table 2). Analogously the C-6 and C-10 chemical shifts are at higher field than C-7 and C-11. This pattern is well reproduced by the assignment hypothesis **2a**, presenting MAE values for ^1H and ^{13}C of 0.15 and 0.61 ppm against 1.9 and 16.5 ppm obtained for **2b** (Table 2). The $|\Delta\delta|$ for the calculated ^1H and ^{13}C chemical shifts of **2a** are lower compared to the values of **2b**. Indeed, we observed $|\Delta\delta|$ of H-6, H-7, H-10 and H-11 for **2a** are 0.09, 0.20, 0.09 and 0.20 ppm vs. the equivalent values for **2b**: 0.76, 0.47, 0.75 and 0.46 ppm. The $|\Delta\delta|$ of C-6, C-7, C-10 and C-11 for **2a** are 1.6, 2.4, 1.7 ad 2.1 ppm against the lager values of **2b** 18.4, 14.4, 18.5 and 14.7 ppm.

Table 2. Comparison of calculated vs. experimental ^1H and ^{13}C NMR chemical shifts of hypothetical assignments **2a** and **2b** in DMSO.

position	^1H (ppm)					^{13}C (ppm)				
	2a			2b		2a			2b	
	δ_{calcd}	δ_{exp}	$ \Delta\delta ^{\text{a}}$	δ_{exp}	$ \Delta\delta ^{\text{a}}$	δ_{calcd}	δ_{exp}	$ \Delta\delta ^{\text{a}}$	δ_{exp}	$ \Delta\delta ^{\text{a}}$
6	7.23	7.32	0.09	7.99	0.76	129.8	128.2	1.6	111.4	18.4

7	7.79	7.99	0.20	7.32	0.47	113.8	111.4	2.4	128.2	14.4
10	7.18	7.27	0.09	7.93	0.75	130.1	128.4	1.7	111.6	18.5
11	7.73	7.93	0.20	7.27	0.46	113.7	111.6	2.1	128.4	14.7
MAE^b		0.15		0.61				1.9		16.5

^a $|\Delta\delta| = |\delta_{\text{exp}} - \delta_{\text{calcd}}|$, absolute differences for experimental versus calculated ¹H and ¹³C NMR chemical shifts. ^bMAE = $\Sigma[|\delta_{\text{exp}} - \delta_{\text{calcd}}|]/n$.

We proceeded calculating the heteronuclear coupling constants for **1** and **2** (Table 3, see experimental section for details). Concerning **1**, we found that the calculated long-range coupling $^4J_{\text{C}_{12\text{a}}\text{-H}_{10}}$ is larger (about twice) than $^3J_{\text{C}_{12\text{a}}\text{-H}_{11}}$ value (Table 3). The other four-bond coupling constants of the spin system C-4a—H-2 and C-8a—H-6 present similar values compared to $^4J_{\text{C}_{12\text{a}}\text{-H}_{10}}$. The same observations could be made for **2**. The $^4J_{\text{C-H}}$ values of the spin system C-4a—H-2, C-8a—H-6 and C-12a—H-10 are 1.4 Hz, 1.4 Hz and 1.5 Hz, respectively. The three-bond couplings of the spin system C-8a—H-7 and C-12a—H-11 are 0.8 Hz and 0.7 Hz, respectively. The theoretical outcomes are in qualitative agreement with the experimentally observed correlations in the HMBC spectra of **1** and **2**, suggesting **1a** and **2a** as the correct chemical shift assignment hypotheses. Indeed, only the $^4J_{\text{C-H}}$ correlations are clearly observable in the HMBC spectra. On the contrary, the $^3J_{\text{C-H}}$ are <1 Hz in size and are not experimentally observed. For the hypothesis **1b** and **2b** the $^3J_{\text{C-H}}$ should be experimentally observable contrasting with the predicted values that are <1 Hz, whereas the $^4J_{\text{C-H}}$ couplings should not be observed despite the calculated constants are >1 Hz.

Table 3. Calculated heteronuclear coupling constants (Hz) for **1** and **2** in DMSO and qualitative comparison with experimental data.

	1		2		
	calc	exp	calc	exp	
$^3J_{\text{C}_{12\text{a}}\text{-H}_{11}}$	0.8	not observed	$^3J_{\text{C}_{12\text{a}}\text{-H}_{11}}$	0.7	not observed
$^4J_{\text{C}_{12\text{a}}\text{-H}_{10}}$	1.5	observed	$^4J_{\text{C}_{12\text{a}}\text{-H}_{10}}$	1.5	observed
$^4J_{\text{C}_{4\text{a}}\text{-H}_2}$	1.5	observed	$^4J_{\text{C}_{4\text{a}}\text{-H}_2}$	1.4	observed

$^4J_{C8a-H6}$	1.3	observed	$^4J_{C8a-H6}$	1.4	observed
			$^3J_{C8a-H7}$	0.8	not observed

Overall, the calculated chemical shifts and heteronuclear coupling constants support as resonance assignments the hypothesis **1a** and **2a**, reported in Table 4.

Table 4. 1H and ^{13}C NMR (ppm) data (400 and 100 MHz, DMSO- d_6) of **1** and **2**.

1					2				
position	δ_H	δ_C	COSY	HMBC	position	δ_H	δ_C	COSY	HMBC
1					1				
2	7.36	129.7		C-3, C-4a, C-12a	2	7.37	129.1		C-3, C-12a
3		95.3			3		95.0		
4					4				
4a		136.4			4a		135.3		
5					5				
6	7.40	129.5		C-4a, C-7, C-8a	6	7.32 (d, 1.6 Hz)	128.2	H7	C-4a, C-7, C-8a
7		95.7			7	7.99 (d, 1.6 Hz)	111.4	H6	C-4a, C-6
8					8				
8a		135.6			8a		135.7		
9					9				
10	7.31 (d, 1.6 Hz)	128.7	H-11	C-8a, C-11, C-12a	10	7.27 (d, 1.7 Hz)	128.4	H11	C-8a, C-11, C-12a
11	7.96 (d, 1.6 Hz)	111.7	H-10	C-8a, C-10	11	7.93 (d, 1.7 Hz)	111.6	H10	C-8a, C-10
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7 **Conclusion**

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9 The recently investigated mono- (**2**) and di-bromo (**1**) derivatives of triimidazo[1,2-*a*:1',2'-*c*:1'',2''-
10 *e*][1,3,5]triazine present a rich and diverse photoluminescent behavior with emissions going from
11 dual fluorescence, molecular phosphorescence to supramolecular room temperature ultralong
12 phosphorescence. The gaining interest towards solid state luminogens prompt to further explore
13 new derivatives of this class of organic compounds. Thus, we structurally investigated **1** and **2** by
14 standard 1D and 2D NMR experiments. As the NMR analysis led to two hypothesis of chemical
15 shift assignments, we integrated the experimental data by QM calculations of NMR parameters
16 disclosing the right chemical shift assignments for **1** and **2**. The theoretical investigations
17 highlighted that some structural moieties of **1** and **2** presented $^4J_{C-H}$ larger two fold $^3J_{C-H}$. In details,
18 the $^4J_{C_{12a}-H_{10}}$ of **1** and **2**, along with $^4J_{C_{8a}-H_6}$, are >1 Hz and observable in the HMBC spectra.
19 Conversely, the three-bond correlation between C-12a and H-11 of **1** and **2**, and C8a and H-7 are <1
20 Hz and result not distinguishable from the noise. These outcomes could be very useful as structural
21 reference for organic synthesis and characterization by routine NMR of new congeners of this
22 intriguing class of molecules.
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44 **Experimental sections**

45 **NMR measurements**

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47 **1** and **2** were synthesized and characterized as reported in the literature.^[11]

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49 NMR measurements were performed at 300 K on a Bruker AVANCE-400 instrument (400 MHz).

50
51 Chemical shifts are reported in parts per million (ppm) and are referenced to the residual solvent
52 peak (DMSO, 1H 2.50 ppm, ^{13}C 39.5 ppm). Mass spectra were recorded on a Thermo Fisher LCQ
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54 Fleet Ion Trap Mass Spectrometer equipped with UltiMate™ 3000 HPLC system.
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3,7-dibromotriimidazo[1,2-a:1',2'-c:1'',2''-e][1,3,5]triazine (1)

NMR data (DMSO-d₆, 300 K, δ , ppm): ¹H NMR 7.97 (1H, d, J = 1.6 Hz), 7.41(1H, s), 7.36 (1H, s), 7.31 (1H, d, J = 1.6 Hz); ¹³C NMR 136.7, 136.4, 135.7, 129.7 (CH), 129.4 (CH), 128.7 (CH), 111.7 (CH), 95.8 (CBr), 95.4 (CBr).

MS (ESI-positive ion mode): m/z 357.1 [M+H]⁺

3-bromotriimidazo[1,2-a:1',2'-c:1'',2''-e][1,3,5]triazine (2)

NMR data (DMSO-d₆, 300 K, δ , ppm): ¹H NMR 7.99 (1H, d, J = 1.6 Hz), 7.93 (1H, d, J = 1.7 Hz), 7.37 (1H, s), 7.32 (1H, d, J = 1.6 Hz), 7.27 (1H, d, J = 1.7 Hz); ¹³C NMR 136.8, 136.1, 135.7, 129.5 (CH), 128.8 (CH), 128.6 (CH), 112.0 (CH), 111.9 (CH), 95.5 (CBr).

MS (ESI-positive ion mode): m/z 277.1 [M+H]⁺

Computational studies

The molecular structures of the compounds **1** and **2** were built through the Build Panel of Maestro (version 11). Their geometries were refined by means of the Polak-Ribier conjugate gradient algorithm (maximum derivative less than 0.001 kcal/mol), using OPLS3 force field^[23] and a constant dielectric term (ϵ = 48) to mimic the presence of DMSO.^[24]

The obtained 3D structures of **1** and **2** from molecular mechanics methods, were further refined at the DFT theoretical level by using MPW1PW91 functional and the 6-31G(d) basis set.^[25,26] The DFT-optimized structures were used for the single-point ¹H and ¹³C chemical shift calculations with the same functional and the 6-31G(d,p) basis set. For these calculations, the integral equation formalism version of the polarizable continuum model (IEFPCM), as implemented in Gaussian (DMSO solvent), was used^[27] to reproduce solvent effects. Calibration of calculated ¹³C and ¹H chemical shifts was performed following the multi-standard approach (MSTD) as reported by

Pellegrinet et al.^[28] In particular, the ¹H and ¹³C chemical shifts were scaled by using benzene as reference compound. The heteronuclear coupling constants for **1** and **2**, were calculated accounting the Fermi contact (FC) contributions by adding tighter polarization functions for the s and d orbitals to the 6-311+G(d,p) basis set with b3lyp functional,^[29] which was accomplished in Gaussian 09 with the “mixed” keyword.

All QM calculations were performed by Gaussian 09 software package.^[30]

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