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I_{PT} : An Index to Rank Molecular Photothermal Agents

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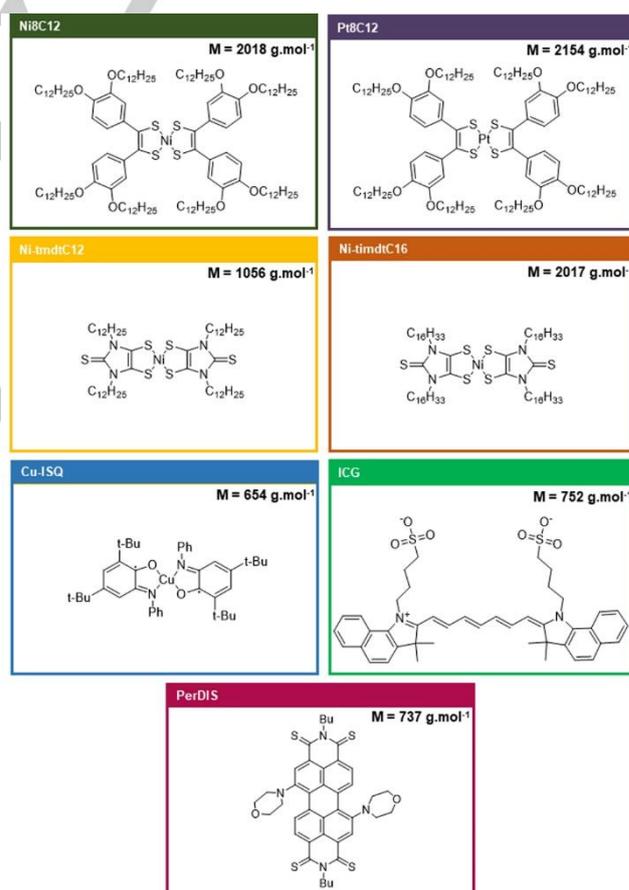
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Abstract: Recently, a large variety of photothermal agents have been developed and are currently under study, owing to their wide range of applications. Nonetheless, the comparison of their relative performance remains a challenge, and it appears that no tool is yet available for rationalizing the data reported in the literature. Indeed, we demonstrate in this paper that neither the temperature increase (ΔT) nor the photothermal efficiency (η) are sufficient to account for the performance of a photothermal agent. From this observation, we propose that a new index, I_{PTmax} , could be used, in order to properly rank molecular photothermal agents according to their efficacy for converting light into heat, in a similar fashion that brilliance is used to compare luminescence properties.

In the last two decades, the photothermal effect has aroused strong interest to develop light-responsive materials such as actuators,^[1] drug delivery system for chemo-photothermal combination cancer therapy^[2] as well as smart materials for water purification^[3] or contrast agents for bioimaging.^[4,5] Many photothermal agents have been used spanning from inorganic nanoparticles to conducting polymers and molecular entities.^[6,7,8,9] The effectiveness of the materials strongly depends on their ability to convert light into heat. However, until now, no real figure of merit has been properly established to account for the photothermal performance of a given compound, especially for well-defined molecular entities. Most of the time, the temperature increase (ΔT being the difference between the steady-state final temperature reached after laser irradiation and the starting temperature before irradiation) is given to attest of the photothermal performance of a compound.^[9] Of course, a good photothermal agent should lead to higher temperature increase. However, the temperature increase doesn't represent a reliable data since it is heavily impacted by parameters intrinsic of the experimental setup such as the concentration of the photothermal agents, the laser power density, the irradiation time, the nature of the solvent, the irradiation wavelength... Consequently, comparison of the photothermal agents according to ΔT would require the measurements to be made using the exact same experimental conditions. In 2007, Roper et al. proposed a system of equations allowing to calculate the photothermal efficiency (η), which reflects the ability of a compound to convert photons into heat, in a similar way that luminescence quantum yield are calculated.^[10] Despite being a big step toward a better characterization of photothermal performances, it appears that the photothermal efficiency is not sufficient for comparing the relative photothermal performances of a list of agents. In fact, some compounds (including some in the present paper) have shown that a high photothermal efficiency when coupled with a low absorption at the irradiation wavelength results in a weak photothermal effect. On the

contrary, a compound showing a weak photothermal efficiency but a strong absorption at the laser irradiation wavelength can lead to a temperature increase far more important. Thus, definition of an intrinsic data that could properly account for the photothermal strength of a compound is still needed. Herein, we demonstrate through the study of seven molecular photothermal agents that a new photothermal index I_{PTmax} , referring to the brilliance used to evaluate luminescence, can be used in order to compare molecular photothermal compounds reliably while limiting experimental constraints.



Scheme 1. Chemical structure, molecular weight and abbreviation of the investigated compounds (the same colour coding will be used all along the manuscript).

The seven molecules selected for this study are presented in Scheme 1. Two dithiolenes complexes formed by complexation of two diphenylethylenedithiolate ligands bearing eight C12 carbon

chains with a nickel (Ni8C12) or a platinum (Pt8C12) metal center as well as two nickel-trithione derivatives carrying C12 (Ni-timdtC12) or C16 (Ni-timdtC16) carbon chains have been selected for their well-known photothermal properties in the NIR region.^[11] A copper derivative (Cu-ISQ)^[12] and a sulfurated perylene derivative (PerDIS)^[13] absorbing in the NIR region have also been investigated as potential photothermal agent. These compounds have been synthesized and purified as previously described (see SI). Finally, the commercially available prototypical photothermal agent, Indocyanine Green (ICG), was introduced in this study.^[14] Equimolar solution of each compound (10 μM) have been prepared in toluene with 1 %v/v of CHCl_3 (or EtOH for ICG).

The absorption spectra of each solution measured between 310 and 1300 nm are presented in Figure 1. The absorption maxima and the molar absorption coefficients are gathered in table S1. All the studied compounds show a single broad absorption band with a maximum in the NIR-I therapeutic window, commonly considered as ranging from 650 to 1000 nm, except for the two Ni-timdt complexes for which the absorption maxima are located at the start in the NIR-II window, around 1010 nm.^[15,16] The Cu-ISQ complex absorbs over a large wavelength range from 600 to 1000 nm but its molar absorptivity remains low (5300 $\text{M}^{-1}\cdot\text{cm}^{-1}$ at 792 nm). The perylene derivative (PerDIS) also has a wide absorption band from 700 nm to 1000 nm, with a maximum molar absorption coefficient of around 18000 $\text{M}^{-1}\cdot\text{cm}^{-1}$. Among the absorbers studied, the dithiolene complexes (Pt8C12, Ni8C12, Ni-timdtC12 and Ni-timdtC16) as well as the ICG have the highest absorbance, with molar extinction coefficients between 40000 and 65000 $\text{M}^{-1}\cdot\text{cm}^{-1}$.

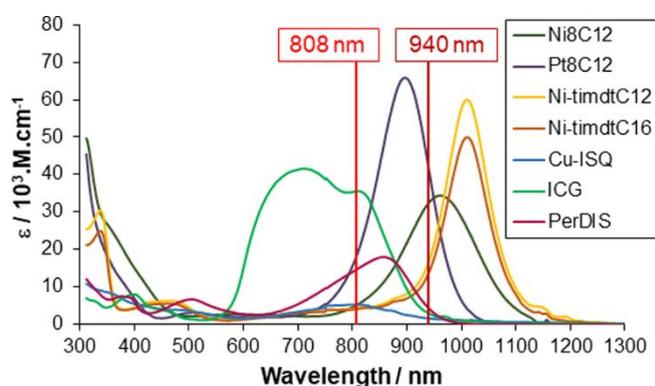


Figure 1. Absorption spectra of the various compounds in toluene at 10 μM (the wavelength of the two lasers used for the photothermal studies are indicated by vertical lines).

The temperature increase of the solutions under laser irradiation and the photothermal efficiency of the compounds were measured using two different lasers emitting at 808 (± 3) and 940 (± 10) nm ($3 \text{ W}\cdot\text{cm}^{-2}$, 10 min ON, 10 min OFF, spot size 0.79 cm^2). The solutions were irradiated during 10 min which is a good compromise to reach a quasi-steady state and avoid

evaporation of the toluene. All the temperature profiles are presented in Figures S1 and S2 and the temperature increases observed at 808 and 940 nm are compiled in Figure S3. All the parameters associated to the photothermal activity of the compounds are summarized in Table 1 and 2. The dithiolene complexes and the PerDIS compound were found stable under laser irradiation, while ICG and Cu-ISQ showed some pronounced photodegradation (Figure S4).

All the solutions showed temperature increases higher than the one measured when irradiating pure toluene, testifying to the photothermal activity of each compounds. As it can be seen in Figure 1, ICG, Cu-ISQ and PerDIS solutions mainly absorb at 808 nm while Ni8C12, Ni-timdtC12 and Ni-timdtC16 solutions mainly absorb at 940 nm. Only the Pt8C12 solution shows good absorption at both wavelengths. As it may be expected, the solutions showing the greatest temperature increase ΔT are those for which the absorbance at the irradiation wavelength is the highest. Thus, no significant temperature increase was observed for the Ni-timdtC12 or the Ni-timdtC16 complexes irradiated at 808 nm, their absorbance at 808 nm being almost zero. No marked temperature increase has also been measured for ICG, PerDIS and Cu-ISQ solutions irradiated at 940 nm. As expected, in regard to the molar absorption coefficient at each wavelength, the temperature increase for Pt8C12 solution is higher at 940 nm ($\Delta T = 39^\circ\text{C}$) than at 808 nm ($\Delta T = 29^\circ\text{C}$). However, it should also be noticed that the temperature increase obtained is not directly proportional to the absorbance of the compound. Indeed, at 940 nm, the ΔT obtained for Ni8C12 is 45°C while it is only 39°C for the Pt8C12 complex, although the absorbance of the Ni8C12 solution at 940 nm ($\epsilon_{940} = 32500 \text{ M}^{-1}\cdot\text{cm}^{-1}$) is lower than that of the Pt8C12 solution ($\epsilon_{940} = 41450 \text{ M}^{-1}\cdot\text{cm}^{-1}$). Likewise, Ni-timdtC12 displays a ΔT of 36°C against 27.5°C for Ni-timdtC16 while their absorbance at 940 nm are very close ($16600 \text{ M}^{-1}\cdot\text{cm}^{-1}$ and $13600 \text{ M}^{-1}\cdot\text{cm}^{-1}$, respectively). Figure 2a clearly shows, that despite a slight linear tendency, there is no real correlation between the value of the molar absorption coefficient measured at the irradiation wavelength and the temperature increase recorded.

Figure 2. Temperature increase measured for each solution under laser irradiation at 808 or 940 nm (a) as a function of the molar absorption coefficient (measured at 808 or 940 nm) or (b) as a function of the photothermal efficiency (808 nm: ICG, Cu-ISQ, Pt8C12, PerDIS; 940 nm: Ni8C12, Pt8C12, Ni-timdtC12, Ni-timdtC16).

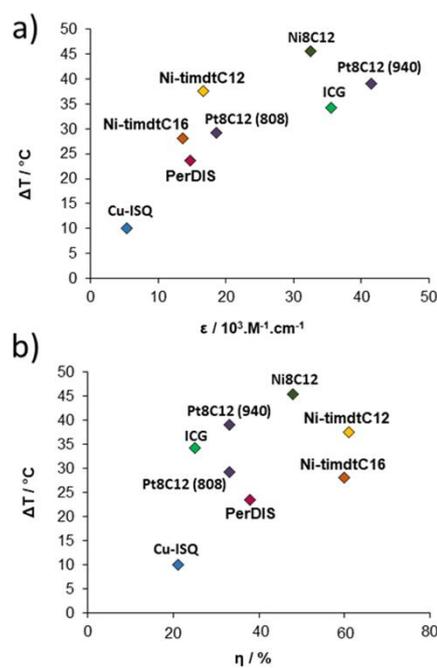


Table 1. Absorbance, temperature increase, photothermal efficiency and heat-transfer coefficient (h) measured for each solution irradiated at 808 nm.

Photothermal agent	Toluene	Pt8C12	Ni8C12	Ni-timdtC12	Ni-timdtC16	Cu-ISQ	ICG	PerDIS
ΔT_{\max} (°C)	6.4	29.2	13.4	7.6	6.8	10.1	34.3	23.6
A_{808}	0	0.179	0.052	0.028	0.017	0.056	0.0325	0.120
η (%)	----	28	36	---	---	21*	25*	38
h (J.s ⁻¹ .K ⁻¹ .cm ⁻²)	0.0159	0.0133	0.0166	0.0182	0.0181	0.0177	0.0142	0.0159

Table 2. Absorbance, temperature increase, photothermal efficiency and heat-transfer coefficient (h) measured for each solution irradiated at 940 nm.

Photothermal agent	Toluene	Pt8C12	Ni8C12	Ni-timdtC12	Ni-timdtC16	Cu-ISQ	ICG	PerDIS
ΔT_{\max} (°C)	1.6	39.1	45.5	37.5	28.1	3.6	5.6	9.8
A_{940}	0	0.440	0.287	0.163	0.123	0.011	0.036	0.047
η (%)	----	33	48	61	60	---	28*	47
h (J.s ⁻¹ .K ⁻¹ .cm ⁻²)	0.0189	0.0169	0.0160	0.0161	0.0169	0.0156	0.0167	0.0178

Some values do not appear in the table because the measured temperature increase and / or absorbance were too low to obtain a reliable result.

(*) photodegradation of the compound leads to a slight underestimation of photothermal efficiency.

The photothermal efficiency of the compounds was also determined by recording the complete temperature profile during the irradiation and after turning off the laser power. The photothermal efficiency was calculated using the equation developed by Roper *et al.* (see SI).^[10] The photothermal efficiency values obtained for each compound, irradiated at 808 and 940 nm, are listed in Tables 1 and 2, respectively. Since the heat dissipation coefficient h is an intrinsic characteristic of the experimental setup, its value varies little from one measurement to another (Tables 1 and 2).

The Ni-timdtC12 and Ni-timdtC16 complexes display a photothermal efficiency of around 60 % at 940 nm. This value is higher than the best energy conversion yields found in the literature for organic structures, such as the recently developed terrylenediimide (41 %),^[17] or the frequently used polypyrrole nanoparticles (35 %).^[18] To our knowledge, these are the highest values reported for molecular photothermal agents, placing them at the level of the most efficient inorganic agents in NIR, such as the tungsten oxides $W_{18}O_{49}$ (59 % at 808 nm),^[19] gold nanorods (21-50 % at 808 nm),^[20] germanium nanocrystals (20-47 % at 770 nm),^[21] or Ti_3C_2 nanosheets (MXene) (30 % at 808 nm).^[22] The substitution of the nickel metal center in Ni8C12 by platinum metal center leads to a decrease of about 15 % in the photothermal efficiency of the complex. The PerDIS compound displays conversion yield comparable to the one of Ni8C12 complex, i.e. around 40 %. This value is consistent with what was found by the team of Zhang *et al.* in their work on the formulation of nanoparticles by self-assembly of an amphiphilic perylene diimide analog (42 %).^[23] However, the extinction coefficient of PerDIS being, at the wavelengths used, lower than that of the other molecules studied, the temperature increase generated is lower than the one observed for Ni8C12. Finally, the ICG and the Cu-ISQ complex display the lowest photothermal efficiencies measured (25 % and 20 % respectively) among the 7 compounds. It is also important to note that the photothermal efficiency values calculated at 808 nm and 940 nm are fairly close for compounds absorbing at both wavelengths, confirming that the photothermal efficiency is

indeed intrinsic to a molecule and does not depend on the irradiation wavelength. The plot of the temperature increase as a function of the photothermal efficiency demonstrates that there is no direct correlation between the temperature increase measured and the photothermal efficiency of the compound (Figure 2b). As an example, the temperature increase measured for Ni8C12 under 940 nm laser irradiation is 45.5 °C while it is only 9.8 °C for PerDIS, despite these two compounds have similar photothermal efficiency (48 and 47 %, respectively). As already stated, when taken independently, neither the photothermal efficiency nor the absorptivity can account for the real photothermal activity of a compound which *in fine* is only revealed by the temperature increase measured under identical experimental conditions.

However, interestingly, by plotting the temperature increase as a function of the product of the molar absorption coefficient at a given irradiation wavelength by the photothermal efficiency, a clear linear relation emerges (Figure 3).

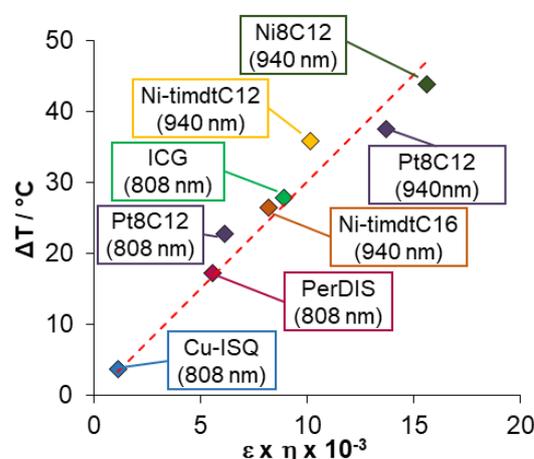


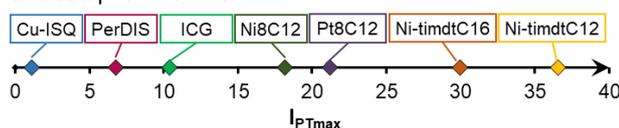
Figure 3. Temperature increase as a function of the product of the molar absorption coefficient by the photothermal efficiency (correlation coefficient of the linear regression $R = 0.97506$).

Thus, based on this observation, a photothermal index (I_{PT}) is proposed to reflect the photothermal activity of a molecular compound and is defined as follow:

$$I_{PT\lambda} = \epsilon_{\lambda} \times \eta \times 10^{-3}$$

$I_{PT\lambda}$ was multiplied by a factor 10^{-3} to obtain more convenient values. This photothermal index allows to properly evaluate the photothermal strength of a molecular compounds. Irradiation of compounds showing high photothermal indexes will lead to higher temperature increases, i.e. higher energy conversion. Thus, $I_{PT\lambda}$ allows to compare photothermal agent irradiated at the same wavelength.

The I_{PTmax} (I_{PT} calculated with ϵ_{max}) could represent reliable quantification of the strength of a photothermal agent, independently of the experimental setup used for the measurement, thus allowing for the direct comparison of the molecular photothermal agents that can be found in the literature. Figure 4 and table S2 show the I_{PTmax} for the molecular agents presently studied. I_{PTmax} allows to compare, in a more general way, the strength of photothermal agents if they are irradiated at their absorption maxima.



$$I_{PTmax} = \epsilon_{max} \times \eta \times 10^{-3}$$

Figure 4. Photothermal efficiency index I_{PTmax} of the various agents studied (based on ϵ_{max} measured in toluene / $CHCl_3$ or EtOH (99: 1, v/v)).

From the I_{PTmax} values, dihiolene complexes appear to be the most efficient photothermal agents among the agents studied, with N,N'-dialkoxyimidazolidine-2,4,5-trithione derivatives showing better performances than the 1,2-diphenylethylene-1,2-dithiolate derivatives, whereas Cu-ISQ has the worse photothermal activity. The photothermal performance of ICG is between the one of 1,2-diphenylethylene-1,2-dithiolate complexes and the one of the perylene derivative. The I_{PTmax} of ICG is 10, the ones 1,2-diphenylethylene-1,2-dithiolate complexes are around 20 and the ones N,N'-dialkoxyimidazolidine-2,4,5-trithione derivatives are above 30.

It should be noticed that despite the fact that the photothermal efficiency is an intrinsic characteristic of the photothermal agent, the molar absorption coefficient will depend on the nature of the solvent. Thus, it is required to compare I_{PTmax} values determined in the same solvent or mixture of solvents.

In conclusion, through the study of seven molecular photothermal agents, a clear relation could have evidenced between the temperature increase measured under laser irradiation and the product of the photothermal efficiency by the molar absorption coefficient ($\epsilon \times \eta$). This product can be compared with the brilliance used in luminescence studies and allows to quantify properly the photothermal activity of a molecular photothermal agent. From this observation, a new photothermal index has been defined $I_{PTmax} = \epsilon_{max} \times \eta \times 10^{-3}$

which provides a reliable tool for quantifying the photothermal strength of molecules and which allows to compare and rank the photothermal agents. The only experimental constraints remaining, in order to be properly compared, is that the I_{PTmax} should be determined in the same solvent. This work and the concept of photothermal brilliance can certainly be extended to inorganic nanoparticles or conducting polymers probably by using the mass extinction coefficient instead of molar coefficient but additional parameters such as the particle size and the surface functionalization will have to be taken into account to properly evaluate the photothermal efficiency. This photothermal index will undoubtedly be of strong interest in the future development and screening of photothermal agents.

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The study of several molecular photothermal agents has allowed to define a new photothermal index I_{PT} , comparable to the brilliance in luminescence, which allow to properly rank the photothermal agents as a function of their ability to convert light into heat, with minimal experimental constraints. The calculation of this photothermal index only implies to know the intrinsic photothermal efficiency of the compound and the molar absorption coefficient at the chosen irradiation wavelength in a given solvent.