

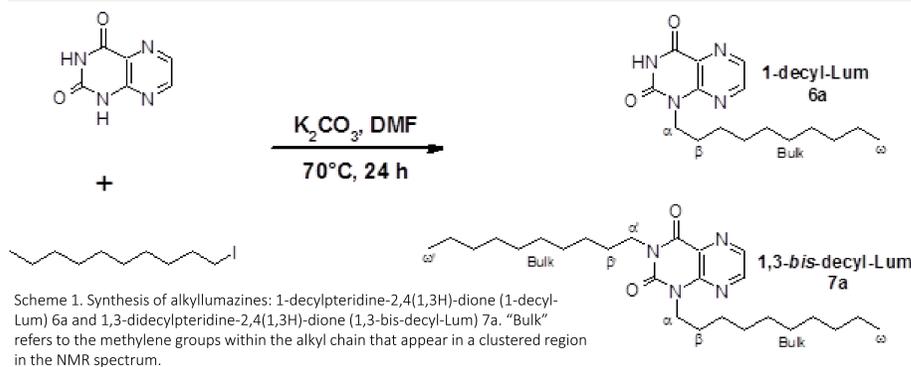
Mono- and Bis-Alkylated Lumazine Sensitizers: Synthetic, Molecular Orbital Theory, Nucleophilic Index, and Photochemical Studies

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ABSTRACT

Mono- and *bis-*decylated lumazines have been synthesized and characterized. Namely, *mono-*decyl chain [1-decylpteridine-2,4(1,3H)-dione] **6a** and *bis-*decyl chain [1,3-didecylpteridine-2,4(1,3H)-dione] **7a** conjugates were synthesized with yields of 26% and 54% respectively, by nucleophilic substitution (S_N2) reactions of lumazine with 1-iododecane, we investigate why only these products were observed..



LUMAZINES

Lumazines are heterocyclic pteridine compounds, present in living systems in different redox states. In the parent form 'Lum', they are poorly soluble in aqueous or organic solvents. Oxidized lumazine derivatives can fluoresce, undergo photooxidation and produce reactive oxygen species, these compounds are efficient photosensitizers and are able to photoinduce the oxidation of biomolecules and cell death.

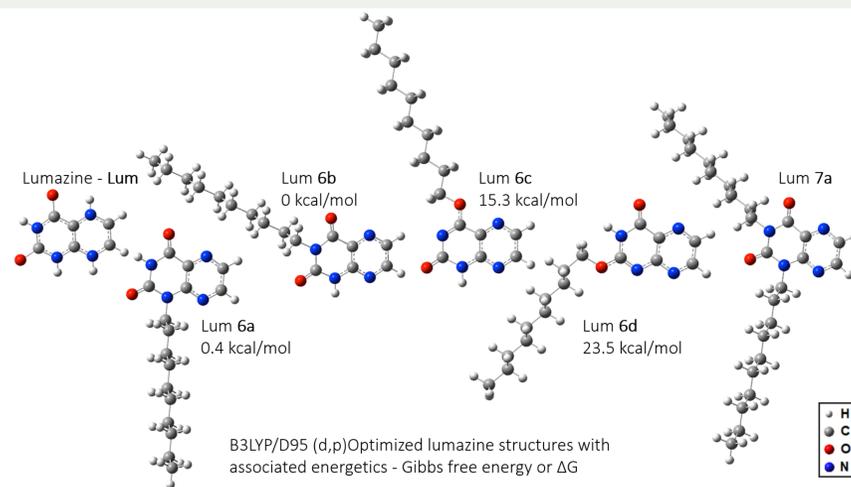
HYPOTHESIS

It was hypothesized that the conjugation of a decyl chain to Lum would increase solubility in organic compounds and allow for study of their photophysical activity, and we now report a study on new alkylated-lumazines, including (i) characterizations, (ii) molecular orbital (MO) and Mayr's nucleophilicity parameter N analyses to help rationalize the alkylation pattern of lumazines (N-decylated but not O-decylated). Pterins, another pteridine derivative, have previously been successfully decylated.

These findings add to the list of alkylation strategies for increasing sensitizer lipophilicity for use in photodynamic therapy.

METHOD

- In the presence of K_2CO_3 Lum reacted with 1-iododecane in DMF at 70 °C for 24h.
- The products were separated by column chromatography and LCMS provided high-resolution mass evidence for the monoalkylation and dialkylation of Lum
- 1D and 2D NMR was performed to elucidate structure
- DFT calculations employed to help predict the alkylation pattern of Lum
- Spectroscopic properties of Lum, **6a** and **7a** were investigated
- Photochemical stabilities of Lum, **6a** and **7a** were evaluated

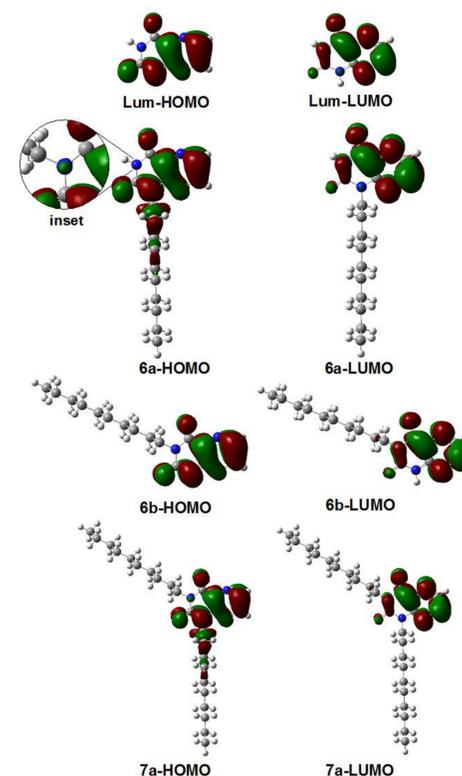


RESULTS and DISCUSSION

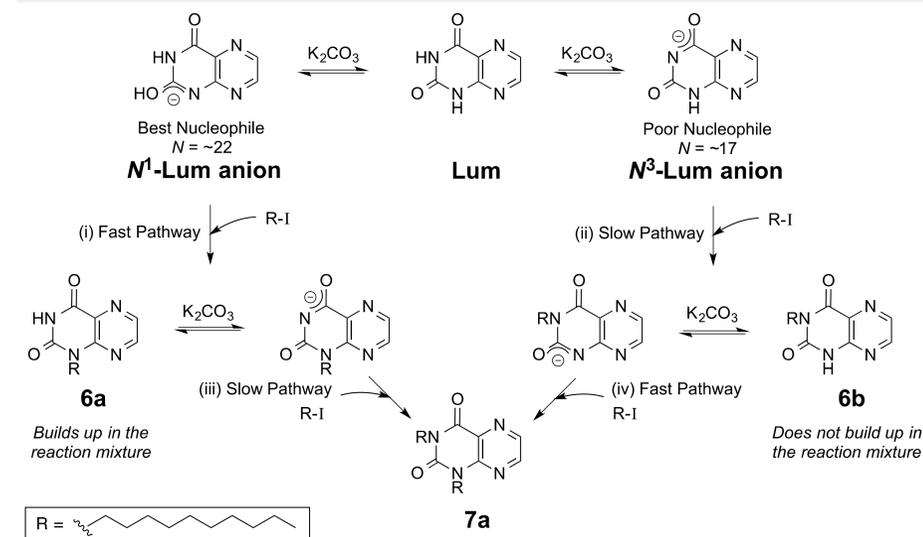
- No O-alkylation of Lum was observed in the reaction, this was intriguing because Lum behaves differently from Ptr (Pterin, another pteridine compound) where O-alkylation is favored.
- We used B3LYP/D95(d,p) calculations to assess the energetics for the decylation of Lum. We find that Lum **6a** and **6b** are nearly isoenergetic. Lum **6a** has a slightly higher energy than **6b** of 0.4 kcal/mol.
- Lumazines **6c** (O2) and **6d** (O1) are substantially higher in energy (23.5 and 15.3 kcal/mol) than **6b**. Concurrently, these lumazines are not observed experimentally.
- DFT calculations also predict the formation of N1,N3-dialkylated **7a**. All other dialkylated combinations (N1,O2, N1,O4, O2,O4, N3,O2, and N3,O4) are less stable by 15.6 to 32.1 kcal/mol

- We then performed B3LYP/D95(d,p) calculations for the highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) on the parent Lum, **6a**, **6b** and **7a**.
- Molecular orbital (MO) calculations show a p-orbital at N1 but not N3.
- Only *after* the alkylation at N1 in **6a**, does a p-orbital on N3 emerge thereby reacting with a second equivalent of 1-iododecane to reach the dialkylated product **7a**

B3LYP/D95(d,p) computed highest occupied molecular orbitals (HOMO) and lowest unoccupied molecular orbitals (LUMO) of Lum, **6a**, **6b**, and **7a**



- Using Mayr's nucleophilicity parameter N we can rationalize that the amide N1 anion will have an N of ~ 22 , which is more nucleophilic compared to the imide N3 anion with an N of ~ 17 , predicting the formation of Lum **6a** over **6b**.
- MO and Mayr's predict the *accumulation* of **6a** and *rapid consumption* of **6b**, which can explain clearly the experimental results.



CONCLUSION

We have now acquired new insight into the alkylation of lumazines;

- We have synthesized and photochemically characterized two decyl chain lumazine conjugates, 1-decylpteridine-2,4(1,3H)-dione **6a** and 1,3-didecylpteridine-2,4(1,3H)-dione **7a**, which form from lumazine through nucleophilic substitution (S_N2) reactions.
- N-Alkylation of lumazine is observed which differs from pterins, where O-alkylation is preferred.
- Compared to Lum, lumazines **6a** and **7a** have substantially higher organic solvent solubilities
- Compared to O-decyl-Ptr, lumazines **6a** and **7a** have lower photostability under UVA irradiation.

DIRECTION

The results with pterins and now with lumazines serve as a reference point for how alkylation patterns at O- vs N- in the former and di- vs mono- in the latter can further advance the lipophilic character of sensitizers. Our work provides a platform on which further research can be built to expand the use of pteridines in membrane-bound photosensitization reactions.

ACKNOWLEDGMENTS

We acknowledge support from the NSF (CHE-1956098)

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