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Review
Ph.D. Dissertation – Marco Farinone

Pyrrole/Pyridine Based Chromophores - Design, Synthesis and Post-Synthetic Reactivity

The candidate has submitted a very thorough study entitled "Pyrrole/Pyridine Based Chromophores - Design, Synthesis and Post-Synthetic Reactivity" which features projects aimed at gaining access to meso-N- and amino acid functionalized BODIPYs and for the preparation of pyridine-containing macrocycles with B-N/N/C motifs. Advancing the functionalization of BODIPYs for inclusion in peptides is an area of high contemporary interest in organic chemistry. Likewise, establishing synthetic routes for B/N-doped polyaromatic hydrocarbons (PAHs) is a cutting edge area of organic materials research. While the BODIPY field is well developed, it is currently expanding into yet unexplored areas of synthetic chemistry and the on-going efforts to develop novel functional PAH organic materials require further advances thereof. Both areas are very challenging projects and the candidate presented a significant body of work, which constitutes an advancement of the field.

Overall, the thesis comprises six main chapters, beginning with an introduction and overview of aromaticity, chromophores, and fluorophores focusing on basic concepts. The following literature section covers synthetic approaches to and modifications of BODIPYs leading over to porpyrinoid macrocycles, pyridine-based macrocycles, and a brief section on proteins and amino acids. Many of the structural systems discussed contain a coordinating boron unit, which forms a central theme of the thesis together with the long term target of introducing the target structures into peptide sequences. This part gives a good introduction well-reasoned state-of-the-art overview of the field and puts this into the context of contemporary developments in the area. Notably, the synthetic literature has been covered excellently giving full credit to related developments. The introduction is didactically well structured, lucid and sets the stage nicely for the subsequent chapters. Similar to the rest of the thesis the section contains only minor errors or typos. Overall the thesis is written with good craftsmanship. Following on are a brief objectives chapter and three main chapters (materials, discussion, conclusions) followed by 'bibliography' (references). The 'purpose' section is rather brief, and lacks some detail on motivation and relevance.

Chapter 3, Materials and Methods, excellently describes the experimental work done and outlines the instrumental techniques used. This section fully details the significant body of experimental work performed by the candidate. Again, this section is well written and formatted. Experiments are described in full detail, allowing repetition of experiments, and most required analytical data are presented. Exceptions are m.p. [lit] for known compounds, CHN analyses and m.p. for new compounds. For the absorption spectra it is not clear to what absorption band corresponds to the one extinction coefficient given. In dye chemistry it is customary to give all data. For several compounds a (semi)systematic name is missing. The reference section (Chapter 6) follows established standards in the discipline. ^{1}H NMR signals are not assigned.

The central part of the thesis (Chapter 4) deals with two synthetic chemistry topics. Chapter 2.1 describes efforts to study the preparation of meso-arylamine substituted BODIPYs and related amino acid derivatives. These could then be fused intramolecularly with DDQ to yield systems with 'quinoline' motifs. These target compounds exhibited an extended aromatic

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system the exact type of which (BODIPY versus dipy) could be controlled by base. While related results are known for porphyrinoids this his fundamental study opens a new branch in BODIPY and dye chemistry. The section contains excellent and very detailed analyses of the molecular structures and switch behavior using single crystal X-ray crystallography, NMR and absorption spectroscopy, and theoretical calculations. This is followed by a section describing a nucleophilic substitution approach to transform meso-chloro-BODIPY (or SMe) into meso-amino acid substituted systems. Similarly to before linkage was achieve via the amino function of the amino acid component. Additionally, O-aryl- and S-linked derivatives were prepared. This served to investigate the influence of the linking heteroatom (S,N,O) on the spectroscopic properties of the BODIPOY unit. Notably, the S-linked 'cystein' derivative exhibited a bathochromic shift of over 100 nm! Two precursor peptides with BODIPY units were prepared but could not be used further due to loss of boron under the resin cleavage conditions. Section 4.2 details the development of syntheses for pyridine containing macrocycles. In a conceptional sense this is related to attempt to prepare bispyridine analogues of the BODIPYs described above, where the pyridine units replace the pyrrole units. Ultimately, the candidate used this approach to prepare macrocycles (**169**,**170**) with three (hetero)aromatic rings. These could then be coupled to dimeric systems such as **175** or be transformed using fusing chemistry into pyrido[2,3-g]quinoline containing dimers (e.g. **173**). These are chemically complex transformations and the section contains detail mechanistic investigations and rational. A final brief section 4.3 describes preliminary studies on preparing furan containing '2.1.1. systems'.

The thesis clearly demonstrates that the candidate has an excellent grasp of the underlying organic chemistry, stereoselective synthesis, and the state-of-the-art of BODIPY and heteromacrocycles. The number of syntheses, characterization experiments and spectroscopic studies is impressive. The thesis clearly advances the field and offers starting points for many subsequent studies, be it in the realm of biological studies with the amino acid derivatives or organic materials with the new macrocycles. This is aided by the experimental section.

Clearly, as established through the body of synthetic and analytical experiments, including mechanistic analyses, the candidate has provided a sufficient body of work for a Ph.D. The far reaching studies into the substitution chemistry of BODIPYs, the astonishing properties of amino acid derivatives and the logically designed and prepared macrocycles yielded impressive results with potential for further studies and the thesis significantly aids the development of the field. The description of the experimental procedures is very good and will allow a repetition of the experiments without problems. Overall, in terms of amount and quality of work, scholarly presentation and insight, the dissertation clearly fulfills the standards of work required.

In summary, I recommend acceptance of the Ph.D. thesis by the examination board.

Sincerely,

Chair of Organic Chemistry, TCD
Dipl.-Chem., Dr. rer. nat., habil., M.A., F.T.C.D.
Hans Fischer Senior Fellow
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