The role of steric hindrance in the intramolecular oxidative aromatic coupling of pyrrolo[3,2-b]pyrroles†

Maciej Krzeszewski,a Paweł Świder,a Łukasz Dobrzycki,b Michał K. Cyrański,*b Witold Danikiewicz* and Daniel T. Gryko*a

The presence of steric hindrance triggers different reaction pathways in the intramolecular oxidative aromatic coupling of tetraaryl-pyrrolo[3,2-b]pyrroles and leads to the formation of a fluorene moiety and a new cationic π-system linked together by a spiro carbon atom. Computational studies elegantly rationalized these results. These previously unknown functional dyes emit red light with reasonable efficiency.

Oxidative aromatic coupling and the Scholl reaction are often the methods of choice in the synthesis of large π-extended scaffolds.1 Indeed, in some cases over 100 C–C bonds are formed from suitable precursors furnishing truly amazing polycyclic aromatic hydrocarbons in one synthetic operation.3 Yet despite being known for almost 150 years, the oxidative aromatic coupling reaction continues to surprise chemists.3 The break-through works of various groups,4 most prominently Müllen5 and Durola,6 have proven that there is often no obvious relationship between steric hindrance and the output of this reaction. A general set of rules which would predict when and how this reaction occurs is still beyond our current reach. Additionally, the mechanistic aspects are still under discussion,1,6,7 although Waldvogel and co-workers have recently made significant progress.8

The extraordinarily easy access to 1,2,4,5-tetraaryl-pyrrolo[3,2-b]pyrroles9 and their intrinsic electron-rich core make them ideal building blocks for the study of oxidative aromatic coupling.10 Our examination of the relationship between the structure of aromatic compounds and the results of oxidative aromatic coupling has provided key information for truly understanding this system as well as the discovery of a new fluorophore. Herein we present the results of this study.

We began our investigation with the preparation of the corresponding 2-arylbenzaldehydes 1b-f using Suzuki–Miyaura coupling. In order to obtain aldehydes 1b–e and 1f, respective bromides (iodides) were reacted with 2-formylphenylboronic acid. To synthesize derivative 1d, 2-bromobenzaldehyde was reacted with 3,5-dimethylphenylboronic acid. Aldehydes 1b-f were synthesized in 60–98% yields (see the ESI†), and they were subsequently used in the synthesis of tetraaryl-pyrrolo[3,2-b]pyrrole, a procedure developed and optimized in our laboratory (Scheme 1).ab Desired products 4a-e were smoothly obtained in yields ranging from 34% to 48% (Scheme 1 and Table 1). The only exception was the reaction of electron-rich aldehyde 3f. The expected compound 4f (based on ESI-MS of the crude reaction mixture) did not form and only tarry products were observed. The most plausible reason behind this result is the low intrinsic stability of hypothetical compound 4f possessing an electron-rich pyrrolo[3,2-b]pyrrole core decorated with electron-donating substituents. Most likely, the oxidation potential of 4f is low enough to facilitate its immediate transformation into polymeric materials in the presence of air.

In accordance with our previous results,10 we subjected 4b–4e to FeCl3 in MeNO2/CH2Cl2. In the case of substrates 4b and 4c, ladder-type π-expanded pyrrolo[3,2-b]pyroles 5b and 5c were formed according to our expectations via double intramolecular oxidative aromatic coupling (Scheme 1 and Table 1). On the other hand, unexpected results were observed for more congested compounds. Derivatives 4d (R1 = R2 = Me) and 4e (R1 = R2 = Br) were reacted with iron(III) chloride and produced very polar red products. Analysis of their NMR spectra led to inconclusive results and eventually the structure of compound 6e was verified via X-ray crystallography. The single crystal structure of compound 6e was established based on the procedures described in the references given in the ESI.† To our surprise the structure of compound 6e contained a spiro carbon atom (Fig. 1).

The structures of 4d and 4e differ from their analogues 4b and 4c in that they possess two substituents (Me or Br) adjacent
system and the new chromophore (Scheme 1 and Fig. 1). The new yields (Table 1). It is noteworthy to add that recently Waldvogel seen spiro derivatives from the second site of the molecule. Interestingly, these unforeseen electron-deficient. Hence the reaction did not occur any further on an already occupied position (rather than unoccupied attacked the aryl substituent in a different way, forming a C–C bond the radical cation formed on the electron-rich pyrrolopyrrole moiety intramolecular oxidative aromatic coupling of cinnamates.\textsuperscript{11} The main reason for the different reactivities of compounds \(4a–c\) and \(4d–e\) spiro five-membered rings are formed, we decided to model both reactions using quantum chemical calculations. Due to the relatively large size of the studied molecules Truhlar’s unrestricted M05-2X DFT functional with the 6-31G(d) basis set has been selected as the method of choice.\textsuperscript{12} Compounds \(4a\) and \(4e\) with removed \(t\)-butyl groups have been selected as the representative models. Calculations were performed using the Gaussian 09 rev. A02 software package.\textsuperscript{13} Full computational details, including Cartesian coordinates of all calculated structures, are available in the ESL.\textsuperscript{†}

As the starting point we assumed that the reaction starts with the formation of a radical cation of the substrate, which subsequently can undergo cyclization through different transition states (TS), resulting in the formation of either a 6-membered ring or a spiro-5-membered ring (Scheme 2). In the next step these intermediates are oxidized, yielding final products: a neutral molecule in the first case and a cation in the second one. The results of the calculations are summarized in Fig. 2. In the case of compound \(7a\) (an analogue of \(4a\) without \(t\)-butyl groups) both the activation energy barriers and the stability of the products favor the formation of a 6-membered ring. A different situation has been observed for tetrabromosubstituted compound \(7e\). In this case the formation of a spiro-5-membered ring is preferred by both TS energy and the relative energy of the product. Both results are in full agreement with the experiments. These results also revealed that it is not possible to tell if the reaction is controlled kinetically or thermodynamically because in both cases the kinetic and thermodynamic products are the same. The main reason for the different reactivities of compounds \(4a–c\) and \(4d–e\) is the steric hindrance. Examination of the calculated structures of compounds \(7a\) and \(7e\) shows that in the case of the latter the formation of the transition state leading to the spiro 5-membered ring is less sterically demanding. A rather surprising observation is that the activation energy of the formation of both transition states for compound \(7e\) is lower than in the case of compound \(7a\), which is obviously less...
sterically crowded. A plausible rationalization for this effect is that compound 7e is already sterically crowded so the difference in steric hindrance between the starting molecule and TS is lower than for compound 7a.

The optical properties of compounds 4b–e and 5b–c were analogous to previously described 4a and 5a (Fig. 3–5 and Table 2). The untypical direction of intramolecular oxidative coupling in the case of 4d and 4e led to the formation of not only a new heterocyclic scaffold but also a new dye. Consequently, both absorption and emission of compounds 6d and 6e were entirely different from those of 5b–c (Fig. 4 and 5 and Table 2). The absorption maxima were in the green region of the spectra. Both compounds emitted red light ($\lambda_{\text{em}}$ 595-606 nm) with moderate intensity.
The Stokes shift for these new dyes was moderate, which probably stems from the difference in the geometry of these molecules between the ground and the excited state. The bathochromically shifted absorption and emission are not apparent in these cases since the novel chromophore is rather small. Due to the steric hindrance the conjugation of the phenyl substituent located at position 5 is most probably minimal (in the ground state).

In conclusion, we have proven that large substituents present at positions adjacent to the site of oxidative aromatic coupling can completely alter the expected reaction pathway. In particular, C–C bonds can form on the already occupied quaternary carbon atom leading to the formation of a five-membered ring and consequently the spiro-product possessing a novel π-conjugated core, the existence of which was unambiguously confirmed by X-ray crystallography. The difference in the course of these two reactions has been post factum rationalized by calculating the thermodynamic stabilization energies of the intermediate structures. As a result of a change of the π-electron system, the absorption and emission of these small dyes are significantly bathochromically shifted versus tetraarylpypyrido[3,2-b]pyrroles or their π-expanded analogues. This unexpected result adds an important piece of information towards understanding the relationship between the structure of the polymeric aromatic compound and the results of its interaction with oxidants.

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Notes and references


13. M. J. Frisch, et al., Gaussian 09, Revision D.01, Gaussian, Inc., Wallingford CT, 2009, for full citation see the ESI†.