

# SYNTHESIS AND OPTIMIZATION OF AROMATICALLY SUBSTITUTED 1,2,4,5-TETRAOXANES AND PEROXY-BODIPY ANALOGS

## Abstract

The aim of this work is to introduce some new synthetic routes and insights into spiro phenyl-substituted 1,2,4,5-tetraoxanes, insights from extending the chemistry of organic peroxides to the BODIPY scaffold and crystallographic studies of interactions of dihydroperoxide groups. In silico studies of spiro phenyl-substituted tetraoxanes provided new bases for potential biologically active compounds against tuberculosis.

We investigated peroxidation of benzaldehyde derivatives to dihydroperoxides (DHP) with hydrogen peroxide and their transformation into potentially biologically active aryl-substituted 1,2,4,5-tetraoxanes (TO). A new synthetic route for the acid-catalyzed peroxidation of deactivated benzaldehydes with electron-withdrawing groups has been developed that enabled preparation of DHP from benzaldehydes with nitro, trifluoromethyl and cyano groups at *p*- and *m*-positions. Large excess of hydrogen peroxide is required for peroxidation, as well as elevated temperature and long reaction times. DHPs were prepared with 2–56 % conversions, while hydroperoxy alcohols and polymeric peroxy compounds were formed as by-products. The products were not isolated due to their instability, but were used directly in a cyclization reaction with 4-methylcyclohexanone to give non-symmetric phenyl-substituted TO with 19–32 % yields. The results suggest that the peroxidation and the order of cyclization reaction strongly affect the yield of TO. When benzaldehydes with electron donating groups are used it is preferred that the DHP is prepared from a carbonyl compound to have better yield of TOs, and vice versa for benzaldehydes with electron withdrawing groups. Optimum conditions for the cyclization reaction between DHP and benzaldehyde were determined to be 0.1 equivalents of acid catalyst and 0 °C, with non-symmetric TO formed in 30 % yield. The substituent on the benzaldehyde also strongly influences the yield of TO and linear correlations with pKa and  $\sigma^+$  were observed ( $R^2$  for pKa= 0,992 and 0,996 for  $\sigma^+$ ). We have shown that when pKa(BH<sup>+</sup>) of the substituted benzaldehyde is lower than –8.13, the benzaldehyde needs to take the role of DHP in the cyclization reaction. The hydrolysis sensitivity study on phenyl substituted tetraoxanes shows that TO with electron-withdrawing groups is resistant to acid hydrolysis while electron-donating groups promote Dakin oxidation to phenols and ketones. The electronic effects of substituents did not affect hydrolysis under basic conditions, with lactone and benzoic acid being the major products of the decomposition of both, TO with electron-withdrawing and electron-accepting groups. We also found that the addition of hydrogen peroxide to the cyclization reaction of DHP and benzaldehyde increased the yield of TO from 26 to 53 %.

Within the structural study, three new DHP derivatives with structurally defined side groups were prepared and their hydrogen bonding ability with the hydroperoxide group was characterized. The interactions of the hydroperoxide group with hydroxyl, carboxyl and nitro groups were investigated by X-ray crystallography. The results show that the hydroperoxide group is an excellent acceptor and donor of hydrogen bonds. The hydroxyl group played only

a role of acceptor, the carboxylic group played both an acceptor and donor role and nitro group was only an acceptor.

In an *in silico* study, we evaluated spiro phenyl-substituted TO as potential biologically active compounds for M tuberculosis. The molecules were composed of »toxic« and »binding« parts joined with a linker. Rv1712, a small cytidine-5'-kinase for which there are no analogs in the human genome, was identified as a suitable target. Initially, docking of 15 isomers of cytidine-5'-monophosphate and 15 analogs of TO with different side groups was performed. The best hits from both groups were then assembled into chimeric molecules and protein-ligand interaction analysis was performed. The results showed that such molecules have potential as biologically active compounds, with binding constant of 9.8  $\mu\text{M}$  for the best hit.

Boron peroxides are rare due to their inherent instability and their chemistry is poorly studied. Our results suggest that we can prepare stable boron peroxides based on BODIPY dyes in good yields. This chemistry enables us to link the photochemical properties of BODIPY dyes with the redox potential of the peroxide moiety. A method has been developed for the preparation of peroxy-BODIPY derivatives with TMSOTf-mediated activation of the BF centre. The use of methoxy BODIPY derivatives significantly increases the yields. Analogs containing  $t\text{BuOO-}$ , octylOO- and hydroperoxide groups were prepared. Moreover, we prepared the first diperoxo-boron species with  $\text{B}(\text{OO}^t\text{Bu})_2$  structural motif in 31 % yield and its cyclic tetraoxane analog in 10 % yield. All the newly prepared mono- and diperoxy-BODIPY derivatives were characterized by cyclic voltammetry, their spectroscopic parameters were measured and their structure and bonding were confirmed and analysed by single crystal X-ray diffraction.