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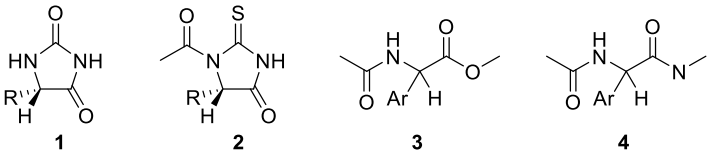
Three aqueous stories: predicting racemisation risk, DNA in sensors and nanoconstruction & taming palladium in catalysis

Niklaas J Buurma,
School of Chemistry, Cardiff University, Cardiff, UK

Racemisation We have shown that enantiomers can show significant differences in key pharmaceutical properties, including cytochrome P450 inhibition and hERG channel blocking.[1] It is therefore of interest to administer the correct enantiomers (or epimers) of drugs. Several types of stereogenic centres are liable to racemise under physiological conditions, potentially leading to significant risk in development and use of pharmaceuticals. A detailed understanding of racemisation processes under physiological-like conditions and a method to predict racemisation risk are therefore required. To address this challenge, we studied a series of compounds, viz. hydantoins **1**, 1-acetyl-2-thiohydantoins **2**, *N*-acetyl arylglycine esters **3**, and *N*-acetyl arylglycine amides **4** (Scheme 1) with stereogenic centres involving a C-H bond.



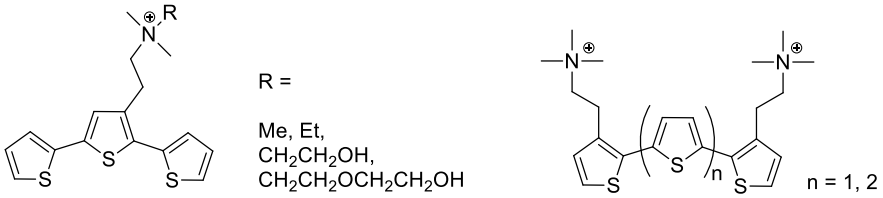
Scheme 1

Compounds **1**-**4** racemise through base-catalysed proton abstraction. We studied the kinetics and mechanism of the racemisation and related H/D exchange of **1**-**4** in aqueous solutions (H_2O and D_2O) in detail, using a range of techniques including ^1H NMR, circular dichroism, and mass spectroscopy as well as optical rotation, and show that racemisation of **1**-**4** proceeds by the S_E2 mechanism. Excitingly, rate constants for H/D exchange and rate constants for

Institut Européen de Chimie et Biologie
2, rue Robert Escarpit - 33607 Pessac, France
Tél. : +33(0)5 40 00 30 38 - Fax. : +33(0)5 40 00 22 15
www.iecb.u-bordeaux.fr

racemisation correlate well with computationally predicted deprotonation energies, allowing quantitative predictions of racemisation risk.

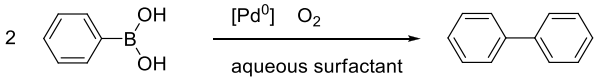
DNA in sensors and nanoconstruction We synthesise cationic conjugated heteroaromatic compounds with interesting optoelectronic properties, including examples in Scheme 2, that bind to nucleic acid structures.



Scheme 2

The DNA binding and self aggregation of these compounds have been studied using various techniques including UV-visible, fluorescence, and circular dichroism spectroscopy, isothermal titration calorimetry, viscometry, competition dialysis and diffusion NMR spectroscopy. To aid these studies, new approaches for the analysis of biophysical interaction data have been developed.[2,3] We have shown that the DNA binding modes of these new DNA binders are very sensitive to the precise structure, and that some of these compounds display selectivity for higher order nucleic acid structures, providing promising prospects for the construction of functional nanostructures.

Taming palladium in aqueous catalysis The oxidative homocoupling of arylboronic acids (Scheme 3) is related to, and a side reaction of, the well-known Suzuki-Miyaura cross-coupling reaction and these reactions share a rate-determining step. We have selected this reaction for detailed kinetic studies in aqueous solutions.



Scheme 3

We have found new kinetic aspects of the oxidative homocoupling reaction of arylboronic acids which include 1) a significant rate-enhancing effect of added cationic surfactants and 2) pH-rate profiles showing maximum reactivity at pH near the pK_a of a series of arylboronic acids. Our results provide a rationale for the requirement for base in coupling reactions involving boronic acids, including the Suzuki-Miyaura cross-coupling reaction, and suggest straightforward optimisation protocols and effective use of enabling technologies for such coupling reactions.

1) *MedChemComm*, **3**, 2012, p. 528-540; 2) *J. Mol. Biol.,* **381**, 2008, 607; 3) *Angew. Chem., Int. Ed.,* **49**, 2010, 3207

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